Appendix I Safety and effectiveness study profiles

Table I.1 Randomised controlled trials – Safety and effectiveness

Authors	Intervention	Study Design	Study Population
Veronesi, Paganelli, Viale, Luini, Zurrida, Galimberti, Intra, Veronesi, Robertson, Maisonneuve, Renne, De Cicco, De Lucia & Gennari, 2003. **Institution** Divisions of Senology, Nuclear Medicine, Pathology, Epidemiology and Anaesthesiology, European Institute of Oncology and the University of Milan School of Medicine, Milan, Italy. **Inclusion/exclusion criteria** Inclusions: patients, 40 to 75 years of age, with invasive carcinoma and no history of any cancer except skin cancer were eligible. Patients with primary breast cancer in whom the tumour was ≤ 2cm in diameter were randomly assigned to undergo, after breast-conserving surgery, either sentinel node biopsy and total axillary dissection (the axillary dissection group) or sentinel node biopsy followed by axillary dissection only if the sentinel node contained metastatic breast cancer (the sentinel node group). Exclusions: patients who had multicentric cancer or who had previously undergone excisional biopsy were not eligible. See table below for further exclusions.	All patients were scheduled to undergo surgery early in the morning. Radiocolloid was injected during the evening before surgery in 410/516 (79.5%). In the other 106/516 (20.5%) patients, the radiocolloid was injected on the day of surgery. **Radioactive colloid and/or dye injection** Five to 10MBq ^{99m}Tc-labelled colloidal human albumin (50 to 200nm diameter) in 0.2ml saline was injected subdermally if the tumour was superficial or peritumorally if the tumour was deep. Lymphoscintigraphy was performed and anterior and antierior-oblique projections of the breast and axilla were obtained to determine the position of the sentinel node. **Removal of sentinel lymph nodes** Four to 20 hours after injection of radiocolloid, SLNB was performed during breast surgery. A gamma detecting probe was used to identify and facilitate the removal of the sentinel node. **Randomisation** Patients were randomly assigned in the operating room to one of the two study groups after it was verified that the sentinel node could be detected and after the size of the tumour was determined. 1) SLNB + AC if SN +ve 2) SLNB + AC **Surgery** The sentinel node was removed through the incision used for tumour resection if the lesion was in the UOQ, or through a separate incision in the axilla if the tumour was in any other quadrant. In the patients assigned to the axillary dissection group, sentinel node biopsy was immediately followed by axillary clearance (all three Berg levels). In the sentinel node group, the operation was concluded if intraoperative analysis of the sentinel node was negative for metastases. If the node was positive, axillary clearance	Randomised controlled trial **Level of Evidence** Level II **Follow-up** Median 46 months **Loss to follow-up** Eight patients died, 6/8 (75.0%) in the axillary clearance group (two form metastatic breast cancer) and 2/8 (25.0%) in the sentinel lymph node biopsy group (one from metastatic breast cancer). **Study Period** March 1998 and December 1999 **Operator Details** Not stated **Outcome measures** Evaluation of side effects 100 consecutive patients from the AC group and 100 consecutive patients that underwent SLNB only were interviewed by physicians from the Breast Department at 6 and 24 months after surgery. Patients were asked to complete a questionnaire concerning the intensity of pain, presence or absence of paraesthesias (assessed by comparing skin sensitivity on the inner and outer upper arms, axillae and chest wall on the operated side with that on the untreated side and sensitivity was recorded as either the presence or absence of numbness), the extent of arm mobility (on a scale from 0%	**Sample Size** 1) 259/516 (50.2%) 2) 257/516 (49.8%) Total: 516 patients **Age** (years) p=0.74 Age | 1) n=259 | 2) n=257 40-45 | 32 (12.4%) | 35 (13.6%) 46-55 | 99 (38.2%) | 88 (34.2%) 56-65 | 92 (35.5%) | 92 (35.8%) 66-75 | 36 (13.9%) | 42 (16.3%) **Type of surgery** All patients underwent quadrantectomy or wide resection, immediately followed by SLNB. **Tumour size** p=0.90 Tumour diameter | 1) n=259 | 2) n=257 <1.0cm | 65 (25.1%) | 65 (25.3%) 1.1-1.5cm | 120 (46.3%) | 123 (47.9%) >1.5cm | 74 (28.6%) | 69 (26.8%) **Stage of disease** p=0.68 Grade | 1) n=259 | 2) n=257 I | 82 (31.7%) | 81 (31.5%) II | 128 (49.8%) | 119 (46.3%) III | 47 (18.3%) | 54 (21.0%) Not stated | 2 (0.8%) | 3 (1.2%) **Tumour histology** p=0.63 Type | 1) n=259 | 2) n=257 Ductal infiltrating | 209 (80.7%) | 212 (82.5%) Lobular infiltrating | 18 (6.9%) | 20 (7.8%) Other | 32 (12.4%) | 25 (9.7%) **Tumour location** p=0.84 Site of tumour | 1) n=259 | 2) n=257 Outer quadrant | 186 (71.8%) | 187 (72.8%)

Continued…

Patients	No. patients
Initially considered for enrolment	**649**
Not eligible	78
Noninvasive breast cancer	12
Tumour diameter >2cm	32
Multicentric disease	26
Sentinel node not revealed by scintigraphy	8
Eligible for enrolment	**571**
Not randomly assigned to a study group	39
Patients decision	25
Sentinel node not evident on preoperative probe-guided inspection	3
Frozen sectioning not feasible	3
Other	8
Randomly assigned to a study group	**532**
Not able to be evaluated	16
Multicentric, bilateral, or extensive multifocal disease	5
Sentinel node not identified at surgery	5
Benign lesion on final histologic examination	4
Metastatic disease	2

(all three Berg levels) was performed immediately.

Pathology
The sentinel node was sent for frozen section immediately after removal.
Sentinel nodes were bisected along the major axis and frozen (nodes <5mm were embedded and frozen uncut). For nodes that were bisected, 15 pairs of sections (4µm thick cut at 50µm intervals) were made in each half of the node. If residual tissue was left, sections were made at 100µm intervals. One section in each pair was stained with H&E, and if the result was ambiguous, the other section was stained for cytokeratins (EPOS Cytokeratin reagent with HRP, Dako) and stained for the monoclonal antibody MNF116.
The nodes removed during conventional axillary dissection were examined by standard techniques (H&E).

[severe restriction] to 100% [no restriction]), and the appearance of the axillary scar (the patient was asked whether the result was good or bad). The circumference (15cm above the lateral epicondyle) of the operated arm was measured and compared with the circumference of the contralateral arm.

Inner or central quadrant	73 (28.2%)	70 (27.2%)

Receptor status p=1.00

Oestrogen	1) n=259*	2) n=257
Positive	237 (91.5%)	236 (91.8%)
Negative	21 (8.1%)	21 (8.2%)

* Oestrogen receptor status was not determined in one patient.

Rate of proliferation p=0.78

	1) n=259	2) n=257
<20% of nuclei dividing	170 (65.6%)	166 (64.6%)
≥20% of nuclei dividing	88 (34.0%)	91 (35.4%)

Peritumoral vascular invasion p=1.00

	1) n=259	2) n=257
Yes	44 (17.0%)	43 (16.7%)
No	215 (83.0%)	214 (83.3%)

Menopausal status
Not stated

Adjuvant therapy
All patients received radiation to the ipsilateral breast over eight weeks (50 Gy, with a 10Gy boost to the skin surrounding the surgical scar).

Patients with unfavourable prognostic characteristics were given systemic adjuvant therapy according to the standard protocols used at the European Institute of Oncology.

Table I.2 Non-randomised comparative studies - Safety and effectiveness

<table>
<tr><th>Authors</th><th>Intervention</th><th>Study Design</th><th>Study Population</th></tr>
<tr>
<td>Baron, Fey, Raboy, Thaler, Borgen, Temple & Van Zee, 2002.

Institution
Breast Service in the Department of Surgery, Memorial Sloan-Kettering Cancer Centre, NY, USA.

Inclusion/exclusion criteria
<u>Inclusions</u>: patients had undergone SLNB alone; had undergone SLNB with total mastectomy (with or without immediate reconstruction); had undergone SLNB with breast-conserving treatment; had any of the above surgeries followed by either an immediate or delayed axillary lymph node dissection; were at least 18 years old.
<u>Exclusions</u>: patients had undergone breast conserving treatment or total mastectomy without SLNB; surgery for prior breast cancer; bilateral breast surgery; preoperative chemotherapy.</td>
<td>1) Sentinel Lymph Node Biopsy
No details given

2) Axillary clearance
Axillary lymph node dissection performed if a positive sentinel node was identified. Patients may have had to return to the operating room for a delayed axillary lymph node dissection.</td>
<td>Non-randomised comparative study

Level of Evidence
Level III-2

Follow-up
6 months

Loss to follow-up
Losses to follow-up were excluded from the results presented. Data presented were from 283 patients who completed the questionnaire at baseline (3-15 days postop.), and at 3 and 6 months.

Study Period
November 1999 to November 2000 (recruitment).

Operator Details
Research assistant recruited patients and reviewed the questionnaire with the patient at baseline, made reminder calls if mailed follow-up questionnaires were not returned.

Outcome measures
Memorial Sloan-Kettering Cancer Center Breast Sensation Assessment Scale (BSAS©) was completed at the initial postoperative visit and mailed to patients at 2 and 5 months following their surgery. The validity of the BSAS© has been previously demonstrated, and the reliability was also being reevaluated in this study.</td>
<td>Sample Size
1) 187
2) 96

Age
1) mean 58, range 27 to 84 years
2) mean 54, range 32 to 85 years

Type of surgery
<table>
<tr><td></td><td>1) n=187</td><td>2) n=96</td></tr>
<tr><td>Breast conserving</td><td>149 (80%)</td><td>55 (57%)</td></tr>
<tr><td>Total mastectomy</td><td>38 (20%)</td><td>41 (43%)</td></tr>
</table>
Stage of disease
<table>
<tr><td></td><td>1) n=187</td><td>2) n=96</td></tr>
<tr><td>0 (DCIS)</td><td>27 (15%)</td><td>0 (0%)</td></tr>
<tr><td>I</td><td>139 (74%)</td><td>8 (8%)</td></tr>
<tr><td>II</td><td>21 (11%)</td><td>87 (91%)</td></tr>
<tr><td>III</td><td>0 (0%)</td><td>1 (1%)</td></tr>
</table>
Tumour histology
Not stated

Tumour location
Not stated

Receptor status
Not stated

Menopausal status
Not stated

Adjuvant therapy
Not stated</td>
</tr>
</table>

Authors	Intervention	Study Design	Study Population
Blanchard, Donohue, Reynolds, Clive & Grant, 2003. **Institution** Departments of Surgery and Pathology, Mayo Clinic, Rochester, Minnesota, USA. **Inclusion/exclusion criteria** Inclusions: consecutive women with early-stage invasive breast carcinoma with clinically negative nodes. Of 1253 consecutive patients, 730 had negative SLNB and 164 had negative SLNB with ALND. Node negative patients were included in study and mailed a survey. Exclusions: patients who died of causes other than due to breast cancer were not included in the data analyses.	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection After an initial phase using blue dye only to localise the SNs, we adopted the use of radiocolloid and blue dye for optimal results. In a volume of 0.4 ml, 0.4 mCi (14.8 MBq) of technetium Tc99m sulphur colloid was injected intradermally either directly anterior to the tumour or along the upper outer aspect of the nipple-areolar complex. Two to 5 ml of isosulfan blue were injected subdermally along the upper outer aspect of the tumour cavity after the tumour had been excised or adjacent to the nipple nipple-areolar complex. Removal of sentinel lymph nodes Lymphoscintigraphy was performed. The position of the first-draining axillary nodes was marked with aid of gamma probe. Approximately 7-15 minutes after injection, a curvilinear incision was made under the axillary hairline and exploration for blue-stained nodes was undertaken. If a mastectomy was performed, the lateral aspect of the mastectomy incision was opened and exploration into the axilla was conducted for blue-stained, radioactive nodes. Pathology Not stated **2) Axillary clearance (SLNB + AC)** No details given	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Mean 2.4 ± 0.9 (SD) years **Loss to follow-up** Questionnaires completed by 776/894 (86.8%) patients. Of the node-negative patients included in the study, eight died of metastatic breast cancer (6 patients had undergone SLNB only and 2 had undergone SLNB with ALND). **Study Period** Patients entered in database between October 1997 to August 31, 2001 **Operator Details** Node negative patients were mailed a survey letter inviting them to participate in the study. Patients who did not respond to survey were mailed a second letter or contacted by phone. Patient medical records were also reviewed for local or distant recurrences or death. **Outcome measures** Following outcomes were analysed: lymphedema of the arm, seroma formation, infection and arm pain.	**Sample Size** 1) 730 (negative SNLB) (685/730 (93.8%) responded) 2) 164 (negative SLNB + AC) (91/164 (55.5%) responded) **Age** 1) mean 61.6 ± 12.5 (SD) years (age at follow-up) 2) mean 58.3 ± 11.6 (SD) years (age at follow-up) **Type of surgery** | | 1) n=685 | n=91 | | Mastectomy | 202 (29.5%) | 20 (22.0%) | **Stage of disease** | | 1) n=682 | 2) n=90 | | 0 | 36 (5.3%) | 0 (0%) | | I | 535 (78.4%) | 68 (75.6%) | | II | 104 (15.2%) | 21 23.3%) | | III | 5 (0.7%) | 1 (1.1%) | **Tumour size** 1) 1.3 ± 0.9 (SD) cm (730 patients) 2) 1.5 ± 1.0 (SD) cm (164 patients) **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** | | 1) n=625 | 2) n=88 | | ER positive | 529 (84.6%) | 75 (85.2%) | | PR positive | 512 (81.92%) | 76 (86.4%) | **Menopausal status** Not stated **Adjuvant therapy** | | 1) | 2) | | Radiation | 439/665 (66.0%) | 67/89 (75.3%) | | Chemotherapy | 161/631 (25.5%) | 28/84 (33.3%) |

Authors	Intervention	Study Design	Study Population
Burak, Hollenbeck, Zervos, Hock, Kemp & Young, 2002. **Institution** Ohio State University, Columbus, OH, USA **Inclusion/exclusion criteria** Inclusions: patients with tumours 4cm or less in size on preoperative measurement, unifocal disease and no prior chemotherapy or radiation therapy. Informed consent obtained in accordance with the Ohio State University Internal Review Board. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection Patients were injected with filtered 99mTechnitium sulphur colloid around the biopsy cavity or around the tumour (peritumoral). Patients requiring image-guided localization received the colloid through the localization needle or through needles placed for this purpose. Injection was performed at least two hours prior to surgery and lymphoscitigraphy was not routinely performed. After induction of general anaesthesia , isosulfan blue (Lymphazuring, Tyco/US Surgical, Norwalk, Colorado, USA) was injected (peritumoral). After 5-10 minutes the breast was massaged. Removal of sentinel lymph nodes A hand-held gamma detection probe (Neoprobe 2000; Neoprobe, Dublin, Ohio or Navigator; Tyco, Norwalk, Connecticut) was used to identify areas of increase radioactivity in the axilla. An axillary incision was made and the axilla was mapped until the sentinel node was identified. Sentinel nodes were defined as nodes that were radioactive (>2 times counts of background), blue (or had a blue afferent lymphatic) or both. Pathology Frozen section was routinely done on all sentinel nodes and an axillary lymph node dissection was performed if the frozen section was positive. Serial sectioning with H&E staining and IHC for cytokeratin was performed on the sentinel node. Patients with evidence of metastases identified on permanent section (H&E or IHC) underwent a completion axillary node dissection as a second procedure. **2) Axillary clearance (SLNB + AC)** Patients underwent a Level I/II axillary clearance if nodal metastases were detected by frozen or permanent (H&E or IHC) section. If a sentinel node was not identified, AC was performed and the patient was excluded from the study. Some of the patients who underwent SLNB also underwent AC as they were part of the centre's validation study.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Mean 15.3, range 8 to 29 months **Loss to follow-up** Not stated **Study Period** Two year period, times not stated. **Operator Details** Arm measurements were performed by one of two examiners. Hand swelling was subjectively graded by a blinded observer. **Outcome measures** Arm measurements – mid biceps, antecubital fossa, wrist in both arms Hand swelling – subjectively graded as mild, moderate or severe. Questionnaire reporting subjective complaints of arm and shoulder pain and numbness, number of infections requiring antibiotics, and the time missed from work of activities of daily living as a result of the surgical procedure. Patients filled out questionnaires at a minimum of 6 months post completion of radiation.	**Sample Size** 1) 48 patients 2) 48 patients **Age** p=0.09 1) mean 59.5 (± 11.5) years 2) mean 55.7 (± 11.4) years **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** All patients received whole breast irradiation after surgery. | | 1) | 2) | | Chemotherapy | 20% | 58% |

<table>
<tr><th>Authors</th><th>Intervention</th><th>Study Design</th><th>Study Population</th></tr>
<tr>
<td>Chirikos, Berman, Luther & Clark, 2001.

Institution
H. Lee Moffitt Cancer Center and Research Institute; Center for Health Outcomes Research, University of South Florida.

Inclusion/exclusion criteria
<u>Inclusions</u>: female patients diagnosed with any histologically confirmed cancer of the breast.
<u>Exclusions</u>: patients who did not undergo any surgery; patients treated by blood/bone marrow transplantation; patients diagnosed at the most advanced disease stage (IV) (excluded to reduce effects of confounders).</td>
<td>Information was extracted from two databases of the H. Lee Moffitt Cancer Center; the charge/billing system and the cancer registry.

Charge/billing system; enters all inputs/resources (apart from physician services) used to treat cancer center patients in inpatient and all outpatient settings. This cumulative record extends over the follow-up period of 44 months or until death, which ever comes first. The authors simplified the analysis by focusing on the total charges for each patient over the period they are observed.

Left-side censoring biases – to eliminate concern from either the timing of events and/or treatment costs incurred at other institutions, the study population was restricted to patients who were diagnosed and then received their first course of therapy over the study period, at the study centre. Right-side censoring biases – to minimize, authors excluded patients diagnosed after March 1 1998 to ensure that all surviving patients have been followed for a reasonable period of time.

1) Sentinel Lymph Node Biopsy (SLNB)
The charge/billing database was used to identify breast cancer patients who underwent SLNB. The center usually bills for lymphoscintigraphy, the intraoperative procedure and the sulfur colloid – authors identified SLNB women in the study population who had numbers for these three billing items on their billing record.
A double check was performed using the research administration database, which documents whether and when patients participated in any research protocol, in order to identify patients enrolled in any lymphoscintigraphic protocol. Information on these patients was used to validate the charge codes in the billings file.

2) Axillary clearance (not SLNB)
Note: these patients may not have had AC, but they definitely have not had SLNB.</td>
<td>Non-randomised comparative study

Level of Evidence
Level III-3

Follow-up
44 months (or until death)

Loss to follow-up
Not applicable

Study Period
August 1 1995 to March 1 1998

Operator Details
Not stated

Outcome measures
Costs, death, recurrence, quality adjusted survival.</td>
<td>Sample Size
1) 555 patients
2) 256 patients

Age
Median 58 years

Type of surgery
Not stated

Stage of disease
<table><tr><td>0</td><td>19%</td></tr><tr><td>I</td><td>43%</td></tr><tr><td>II</td><td>33%</td></tr><tr><td>III</td><td>5%</td></tr></table>
Tumour histology
Not stated

Tumour location
Not stated

Receptor status
Not stated

Menopausal status
Not stated

Adjuvant therapy
<table><tr><td>Surgery alone</td><td>341/811 (42%)</td></tr><tr><td>Surgery plus radiation therapy</td><td>122/811 (15%)</td></tr><tr><td>Other pairs of therapies</td><td>162/811 (20%)</td></tr><tr><td>Other combination therapies</td><td>178/811 (22%)</td></tr></table></td>
</tr>
</table>

Authors	Intervention	Study Design	Study Population
Gemignani, Cody, Fey, Tran, Venkatraman & Borgen, 2000. **Institution** Department of Surgery and Department of Biostatistics; Memorial Sloan-Kettering Cancer Center, New York, NY, USA. **Inclusion/exclusion criteria** Inclusions: T1 tumours, breast conservation therapy, absence of any clinical suspicion of lymph node metastases. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SNLB)** Prospective SLN database was used to identify the first 50 consecutive patients meeting the criteria who underwent SLNB at Memorial from July 1 1997 to June 30 1998. 99mTc-unfiltered sulphur colloid (CIS-US, Inc, Bedford, MA, USA) and isosulfan blue dye (Lymphazurin; Senith Parentals, Rosemount, IL, USA) as reported in Hill et al., 1999. Excised SLNs evaluated by intraoperative frozen-section analysis. If metastases were detected, and AC was performed. The SLN is subjected to serial sectioning and further IHC staining after the procedure. If final pathologic examination by H&E or IHC staining reveals metastases, the patient is offered AC at a later date. **2) Axillary clearance (AC)** A similar cohort of 50 patients who underwent conventional AC between July 1 1997 and June 30 1998 were chosen (matched by age, tumour size, and lymph node status).	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-Up** Not applicable **Loss to follow-up** Not applicable **Study Period** July 1 1997 to June 30 1998 (this period was chosen because it was one where SLNB was performed without backup AC, but the database included data from October 1996 to February 2000). **Operator Details** All procedures were performed by attending surgeons of the Breast Service, with surgical fellows or residents acting as first assistants. **Outcome measures** Retrospective chart review to obtain clinical information (operative and length-of-stay data for both groups).	**Sample Size** 1) 50 patients (3 subgroups; Group 1 composed of patients with negative nodes (n = 37), Group 2 consisted on those (n = 5) with negative nodes on frozen-section analysis and micrometastases on subsequent IHC stains and Group 3 was made up of those (n = 8) with positive nodes on frozen-section analysis). 2) 50 patients **Age** 1) mean 57 years 2) mean 62 years **Type of surgery** Breast conservation therapy **Stage of disease** T1 **Mean tumour size** 1) 1.13cm 2) 1.28cm **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Giuliano, Haigh, Brennan, Hansen, Kelley, Ye, Glass & Turner, 2000. **Institution** Joyce Eisenberg-Keefer Breast Center, Division of Surgical Oncology, Statistical Coordinating Unit, Department of Nuclear Medicine and Department of Pathology, John Wayne Cancer Institute, St John's Health Center, Santa Monica, CA, USA. **Inclusion/exclusion criteria** Inclusions: consecutive patients with invasive breast carcinoma, clinically negative nodes. Exclusions: primary lesions greater than 4cm, multifocal tumours, locally advanced disease, disease diagnosed by large excisional biopsies or formal resections. Note: the patients in the case series by Hansen *et al.* (2002) may be duplicated here.	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection Isosulfan blue dye (1% Lymphazurin; Hirsch Industries Inc., Richmond, VA, USA) was injected around the edge of the lesion, or through the localising needle in the case of a nonpalpable lesion or into the wall of the biopsy cavity if an excisional biopsy had been performed. In the last 6 months of the study, patients with medial hemisphere lesions underwent preoperative breast lymphoscintigraphy to document lymphatic drainage to the axilla. Removal of sentinel lymph nodes Through an axillary incision, blue-stained afferent lymphatics were identified using blunt dissection and traced to all blue-stained sentinel nodes, which were excised for frozen section. Pathology Frozen section, haematoxylin and eosin staining and/or immunohistocytochemistry. **2) Axillary clearance (SLNB + AC)** Patients whose sentinel nodes were tumour free did not undergo axillary clearance. Patients who had a positive sentinel node underwent axillary clearance during the original procedure if diagnosed intraoperatively, or during a second procedure if permanent section of the sentinel node contained tumour cells revealed by haematoxylin and eosin staining and/or immunohistocytochemistry. Closed suction drainage was used for all axillary clearance patients, but not for sentinel node biopsy alone patients.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Median 39 months (minimum 24 months in survivors, maximum 51 months) (Patient's examined at 1, 2 and 4 weeks postop. and then at 6 month intervals. Mammography performed biannually for the first 2 years and then annually). **Loss to follow-up** Not stated **Study Period** October 1995 to July 1997 **Operator Details** Not stated **Outcome measures** Clinical examination, mammography.	**Sample Size** 1) 67 2) 58 **Age** mean 58, range 32 to 89 years **Type of surgery** Segmental mastectomy (breast conservation) 119/125 (95%) Total mastectomy 6/125 (5%) **Stage of disease** 1) n=67 2) n=58 T1a 10 (15%) 2 (3%) T1b 20 (30%) 8 (14%) T1c 27 (40%) 26 (45%) T2 10 (15%) 19 (33%) T3 0 (0%) 3 (5%) (American Joint Committee on Cancer pathologic staging criteria). **Tumour histology** Not stated **Tumour location** UOQ 80/125 (64%) UIQ 13/125 (10%) LOQ 13/125 (10%) LIQ 10/125 (8%) Subareolar 9/125 (7%) **Receptor status** Not stated **Menopausal status** Premenopausal 44/125 (35%) Postmenopausal 81/125 (65%) **Adjuvant therapy** Individualised. Radiation: External-beam radiation recommended after segmental mastectomy. Patients received 46 to 50 Gy to the whole breast as tangential fields, boost to the tumour be of at least 60 Gy. No patient received radiation fields to the axilla. Chemotherapy: Four cycles of doxyrubicin and cyclophosphamide or six cycles of cyclophosphamide, methotrexate and fluororacil (CMF). Hormonal: Tamoxifen

Authors	Intervention	Study Design	Study Population
Golshan, Martin & Dowlatshahi, 2003. **Institution** Department of Surgery, Rush University, Rush Presbyterian St Luke's Medical Center, Chicago, Illinois, USA. **Inclusion/exclusions criteria** Inclusions: patients who had undergone ALND or SLNB and who were at a minimum of one year postoperative. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB only)** Radioactive colloid and/or dye injection Sulphur colloid solution labelled with 1 mCi of technetium 99 was injected under ultrasound guidance around the primary tumour or away from the biopsy site if mapping was performed postlumpectomy. If preoperative scanning failed to show the location of SN, Lymphazurin 1% (isosulfan blue dye) was used in the same manner in 5% of cases. Removal of sentinel lymph nodes Not stated Pathology Not stated **2) Axillary clearance (AC)** No details given All patients undergoing SLNB were not treated with completion ALND regardless of pathological status of the axilla. Surgeon (KD) removed any other suspicious level I lymph node during careful exploration of the axilla after SLNB.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Not stated **Loss to follow-up** Not stated **Study Period** Not stated **Operator Details** Patients were invited to participate during follow-up visits. Informed consent was obtained followed by the performance of detailed history and physical. Operations performed by single surgeon (KD). Collected data were reviewed by the Rush Department of Biostatistics. **Outcome measures** Questions specific to lymphedema and sensory changes were asked, after interview measurements of arm circumference 10 cm above and 10 cm below the olecranon process were taken by a physician. Sensory and ROM examinations were performed. In this series, the difference in arm circumference between the operated and nonoperated side > 3 cm was defined as significant for lymphoedema.	**Sample Size** 1) 77 2) 48 **Age** 1) Mean 53.2 years (at surgery) 2) Mean 52.8 years (at surgery) **Type of surgery** Not stated **Stage of disease** {table} All patients were clinically node negative at time of operation. **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Incidence of postoperative radiation to affected breast {table}

	1) n=77	2) n=48
T1	61 (79.0%)	29 (60.0%)
T2	16 (20.9%)	18 (36.6%)
T3	0 (0.0%)	2 (3.3%)

	1) n=77	2) n=48
Postoperative radiation to the affected breast	70 (91.5%)	37 (76.7%)

Authors	Intervention	Study Design	Study Population
Haid, Köberle-Wührer, Knauer, Burtscher, Firtzsche, Peschina, Jasarevic, Ammann, Hergan, Sturn & Zimmermann, 2002a. **Institution** Department of General and Thoracic Surgery, Department of Nuclear Medicine, Institute of Pathology and Central Radiology Service, Landeskrankenhaus Feldkirch, Akademisches Lehrkrankenhaus der Universität Innsbruck, Feldkirch, Austria. **Inclusion/exclusion criteria** Inclusions: patients with single lesions<5cm and clinically and sonographically negative axillary nodes. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB)** Questionnaire presented to the first 58 women who had undergone SLNB without AC and completed adjuvant radiotherapy and/or chemotherapy. Follow-up included history and clinical examination. Axillary sonography was performed at intervals of 3 months post surgery by a radiologist. Radioactive colloid and/or dye injection Sentinel nodes were labeled by peritumoural injection of radiocolloid (Albu-Res 400µCi in the first 34 patients, later Nanocoll® or Senti-Scint®, 1.6mCi 18-20h prior to surgery). Five to 10 mins prior to surgery 4ml of blue dye (Patent blau V Guebert® 2.5% or Lymphazurin® 1% Isosulfan Blue) was injected peritumorally. Removal of sentinel lymph nodes Details not stated. Pathology Sentinel nodes smaller than 5mm were fixed and embedded uncut. Sentinel nodes >5mm were bisected and multiple sections were made for sentinel nodes >8mm. Four sections were obtained from each node or part of a node at different levels, stained with haematoxylin and eosin and immunohistochemically for cytokeratins (CAM 5.2). (Axillary clearance was omitted after the first 55 SLNB procedures) **2) Axillary clearance (AC)** In 1998 all patients who had undergone axillary clearance between 1993 and 1996 were re-examined for subjective complaints and administered a questionnaire. Pathology All non-sentinel nodes obtained by axillary dissection were routinely processed, nodes up to 8mm were bisected, nodes larger than 8mm were cut to 3mm slices and two haematoxylin and eosin stained sections were prepared from every slice. [**3) Length of Stay** The length of stay of the 57 patients in Group II was compared with that of breast cancer patients, who had undergone SNB and AD or AD from the start for surgical management during the same period (April 1997 to July 2000) because of infiltrated sentinel nodes or clinically involved nodes (n=109)]	Non-randomised comparative study **Level of Evidence** Level III-3 **Follow-up** 1) mean 18, range 5 to 30 months 2) mean 25, range 14 to 60 months **Loss to follow-up** 1) (One of 58 women died from distant metastases, in another four, axillary dissection had been omitted for various reasons – high age, patients request – despite nodal involvement with micrometastases in 3 patients and macrometastases in 1 patient). 2) 177 questionnaires were sent out, 140 were returned and found to be evaluable. **Study Period** 1) Since April 1997 2) Patients who had undergone AC between 1993 to 1996 were reexamined in 1998 **Operator Details** Five surgeons were involved in performing sentinel lymph node biopsy. **Outcome measures** Questionnaire compiled by investigators with questions to possible problems after this kind of treatment based on their clinical experience and the literature cited. Lymphoedema was considered to be present if the arm circumferences differed by more than 2cm (measured proximal and distal to the epicondyle) and if the consistency of the tissue was typical of oedema. Preexisting morbidity in the shoulder was not documented.	**Sample Size** 1) 57 2) 140 [3) 109] **Age:** 1) mean 57, range 39 to 85 years 2) mean 62, range 27 to 86 years **Type of surgery** 1) n= 57: Breast salvaging 50 (87.7%); Mastectomy 7 (12.3%) 2) n=140: Breast salvaging 68 (48.6%); Mastectomy 72 (51.4%) **Stage of disease** 1) mean tumour diameter 17mm 2) mean tumour diameter 26mm **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** 1) n=57: Premenopausal 15 (26.3%); Postmenopausal 42 (73.7%) 2) n=140: Premenopausal 42 (30.0%); Postmenopausal 98 (70.0%) **Adjuvant therapy** (As recommended by the consensus conferences of St. Gallen) 1) n=57: Chemotherapy 16 (28.1%); Hormonal 43 (75.4%); Radiotherapy 47 (82.5%) 2) n=140: Chemotherapy 50 (35.7%); Hormonal 91 (65.0%); Radiotherapy 27 (19.3%) Chemotherapy: six cycles of cyclophosphamide, metothrexate, 5-fluorouracil (CMF) or four cycles of epirubicin and cyclophosphamide. Hormonal therapy: tamoxifen was administered for 5 years Radiotherapy to the axilla was administered to 8 patients in Group I (in these, the severity of arm swelling and of other complaints was not significantly higher).

Authors	Intervention	Study Design	Study Population
Haid, Kuehn, Konstantiniuk, Koberle-Wuhrer, Knauer, Kreienberg & Zimmermann, 2002b. **Institution** Department of General and Thoracic Surgery, Landeskrankenhaus Feldkirch, Austria; Department of Obstetrics and Gynaecology, Krieskrankenhaus Gifhorn, Germany; Department of Surgery II, Landeskrankenhaus Graz, Austria; Department of Obstetrics and Gynaecology, University Medical School Ulm, Germany. Inclusion/exclusion criteria: Inclusions: for SLNB; Single tumours, no clinical or sonographic findings in the axilla. Exclusions: patients with preexisting disease on the operated or the contralateral sides and patients prescribed radiotherapy of the draining axillary nodes. (Note: The SLNB group appears to be an update of Haid, Köberle-Wührer, Knauer, Burtscher, Firtzsche, Peschina, Jasarevic, Ammann, Hergan, Sturn, Zimmermann, 2002a).	**1) Sentinel Lymph Node Biopsy (SLNB)** Patients who had undergone SLNB only within the study period. Radioactive colloid and/or dye injection Indications and technique reported elsewhere (Haid *et al.* 1999). Removal of sentinel lymph nodes Indications and technique reported elsewhere (Haid *et al.* 1999). Pathology Not stated **2) Axillary clearance (AC)** Randomly selected females who were subjected to AC during the study period. Pathology Not stated	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** 2 months post surgery at the earliest **Loss to follow-up** Not stated **Study Period** April 1997 to November 2000 **Operator Details** Not stated. **Outcome measures** Subjective perception of severity of pain, arm swelling, loss of muscle strength and range of motion, using a scaled questionnaire. Objective measurements - limitations in range of motion arm abduction was measured with a goniometer and compared to the contralateral arm (differences of more than 10cm between the two arms was rated as limitation); arm volume calculated from two measurements (10cm below and above the lateral epicondyle; differences of more than 10% between the two arms was rated as oedema); isotonic muscle strength assessed by the maximum angle of abduction when lifting 3kg with arms extended (a difference of more than 20° between the two arms was considered to reflect loss of muscle strength); sensitivity of the inner aspect of the operated arm was measured by touch (and documented as no or yes). Scores were summed (maximum score – 100, patients asymptomatic; the score was reduced as a function of the severity of the subjective and objective scores. (This summation score appears to be previously validated).	**Sample Size** 1) 66 2) 85 **Age** 1) 56.5 years 2) 56.5 years **Type of surgery** | | 1) n=66 | 2) n=85 | | Breast salvage | 60 (90.9%); | 57 (67.1%); | | Mastectomy | 6 (9.1%) | 28 (32.9%) | **Stage of disease** p=0.066 | Grade | 1) n=66 | 2) n=85 | | 1 | 16/66 (24.2%) | 10/85 (11.8%) | | 2 | 32/66 (48.5%) | 40/85 (47.1%) | | 3 | 18/66 (27.3%) | 35/85 (41.2%) | 1) Mean tumour diameter 17.4mm 2) Mean tumour diameter 23.3mm (p=0.019) **Tumour histology** p=0.02 | | 1) n=66 | 2) n=85 | | Invasive ductal | 49 (74.2%) | 65 (76.5%) | | Invasive lobular | 5 (7.6%) | 15 (17.6%) | | Other | 12 (18.2%) | 5 (5.9%) | **Tumour location** Not stated **Receptor status** | | 1) n=66 | 2) n=85 | | Positive | 57 (86.4%) | 67 (78.8%) | **Menopausal status** | | 1) n=66 | 2) n=85 | | Premenopausal | 22 (33.3%); | 22 (25.9%) | | Postmenopausal | 44 (66.7%) | 63 (74.1%) | **Adjuvant therapy** | | 1) n=66 | 2) n=85 | | Chemotherapy | 18 (27.3%) | 55 (64.7%) (p<0.001) | | Hormonal therapy | 49 (74.2%) | 55 (64.7%) | | Postoperative radiotherapy | 51 (77.3%) | 64 (75.3%) |

Authors	Intervention	Study Design	Study Population
Leidenius, Lappänen, Krogerus & von Smitten, 2003. Location: Breast Surgery Unit, Unit of Nuclear Medicine and Department of Pathology, Maria Hospital, Helsinki University Hospital, Helsinki, Finland. Inclusion/exclusion criteria Inclusions: none stated Exclusions: patients were excluded if the schedule of the day before the operation did not allow the preoperative examination in their cases.	**1) Sentinel Lymph Node Biopsy (SLNB)** Patients with uninvolved SNs received no AC (n=44; five patients had sentinel node metastases undetected by frozen section and four underwent AC later, one patient had an uninvolved SN but a positive margin after breast conserving surgery, and underwent a mastectomy and immediate breast construction later). Radioactive colloid and/or dye injection Lymphoscintigraphy was performed on the day before surgery, 4hr after intratumoral injection of 80-100MBq ^{99m}Tc-labeled human albumin colloid in 0.2ml. Patent blue dye (1ml) was injected intratumorally at least 5min prior to incision. Removal of sentinel lymph nodes Sentinel nodes were located using a gamma probe and by locating blue stained lymphatic vessels and nodes. All radioactive and blue nodes were removed. After SLNB, palpation of the open axilla was performed and all enlarged or hard lymph nodes were removed. Pathology Frozen section, but other histology not specifically stated. **2) Axillary clearance (SLNB + AC)** Level I to II AC was performed during the same operation in 36 patients (when frozen section of the SN showed metastases (n=30); when sentinel nodes were not identified (n=5); when multifocal carcinoma was detected (n=1)). Pathology Not stated	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-Up** 2 weeks postoperatively; 3 months postoperatively. **Loss to follow-up** Not stated **Study Period** January 30 2001 to June 21 2001 **Operator Details** Surgeon conducted preoperative and 2 weeks postoperative examinations. Physiotherapist conducted examination 3 months postoperatively. SLNB and AC performed by two experience surgical oncologists (Leidenius or von Smitten). **Outcome measures** Pre- (day before surgery) and postoperative (at 2 weeks postoperatively) physical examination by surgeon and physiotherapist. Three month postop. examination by a physiotherapist. Diagnostic criteria for axillary web syndrome was "the presence of palpable and visible cords of tissue in the axilla in maximal shoulder abduction, with or without associated pain or shoulder range-of-motion limitation". Goniometer used to measure range of shoulder flexion and abduction and reasons for limited movements were registered.	**Sample Size** 1) 49 2) 36 **Age** 1) median 61, range 36 to 82 years 2) median 52, range 39 to 76 years **Type of surgery** 1) n=49: Breast conserving 39 (79.6%) 2) n=36: Breast conserving 26 (72.2%) **Stage of disease** 1) median 15, range 3 to 42mm 2) median 16, range 5 to 60mm **Tumour histology** 1) n=49: Ductal carcinoma 20 (40.8%); Lobular carcinoma 15 (30.6%); Other 14 (28.6%) 2) n=36: Ductal carcinoma 15 (41.6%); Lobular carcinoma 15 (41.6%); Other 6 (16.7%) **Tumour location** 1) n=49: UOQ 29 (59.2%); LOQ 7 (14.3%); UIQ 9 (18.4%); LIQ 2 (4.1%); Central 2 (4.1%) 2) n=36: UOQ 14 (38.9%); LOQ 7 (19.4%); UIQ 10 (27.8%); LIQ 3 (8.3%); Central 2 (5.6%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Peintinger, Reitsamer, Stranzl & Ralph, 2003. **Location** Gynaecological Department, General Hospital Bruck/Leoben, Leoben; Department for Breast Diseases, General Hospital Salzburg, Salzburg; Department for Radiotherapy, University Medical School of Graz, Graz, Austria. **Inclusion/exclusion criteria** Inclusions: consecutive patients with breast cancer stage I or II, breast conserving surgery in all patients, patient's age between 18 and 80 years, no physical or mental comorbidity, performance status 0 and informed consent. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection Peritumoral injection, 16 to 18 hours prior to surgery, of ^{99m}Tc-labelled albumin (Nanocoll®; Sorin Biomedica, Saluggia, Italy) and subareolar subcutaneous injection, 5 minutes prior to incision, of Patent blue dye (Patent Blue V®; Laboratoire Guerbet, Aulnay-sous-Bois, France). Removal of sentinel lymph nodes Hot and blue nodes were removed Pathology Frozen section was performed immediately **2) Axillary clearance (SLNB + AC)** Radioactive colloid and/or dye injection Peritumoral injection, 16 to 18 hours prior to surgery, of ^{99m}Tc-labelled albumin (Nanocoll®; Sorin Biomedica, Saluggia, Italy) and subareolar subcutaneous injection, 5 minutes prior to incision, of Patent blue dye (Patent Blue V®; Laboratoire Guerbet, Aulnay-sous-Bois, France). Removal of sentinel lymph nodes Hot and blue nodes were removed Pathology Frozen section was performed immediately, and if positive AC was performed immediately. Before the study was started, a surgical protocol was implemented in order to minimise differences in technique: similar incisions, similar anatomic dissections and similar drainage catheters were used.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Before surgery (t1), one week after discharge (t2), 9 to 12 months after surgery (t3) **Loss to follow-up** Not stated **Study Period** September 2000 and March 2002 **Operator Details** Not stated **Outcome measures** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30; validated) and BR23 (QLQ-BR23; validated), the Mc Gill Pain Questionnaire (German version; validated), Karnofsky performance scale status (KPS; validation not stated) and the visual analogue pain scale. Patients underwent goniometric measurement of shoulder/arm mobility (shoulder flexion, shoulder extension, shoulder abduction, horizontal abduction, horizontal adduction).	**Sample Size** 1) 25 2) 31 **Age** p=0.27 1) mean 61.4 years 2) mean 57.7 years **Type of surgery** 1) n=25: Breast conserving: 25 (100%) 2) n=31: Breast conserving: 31 (100%) **Stage of disease** 1) n=25: pT1: 17 (68.0%); pT2: 8 (32.0%) 2) n=31: pT1: 23 (74.2%); pT2: 8 (25.8%) p: pT1: 0.62; pT2: 0.62 **Tumour histology** 1) n=25: Invasive ductal: 14 (56.0%); Invasive lobular: 6 (24.0%); Invasive ductal and intraductal: 5 (20.0%) 2) n=31: Invasive ductal: 20 (64.5%); Invasive lobular: 2 (6.5%); Invasive ductal and intraductal: 9 (29.0%) p: Invasive ductal: 0.52; Invasive lobular: 0.07; Invasive ductal and intraductal: 0.44 **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** 1) n=25: Premenopausal: 5 (20.0%); Postmenopausal: 20 (80.0%) 2) n=31: Premenopausal: 11 (35.5%); Postmenopausal: 20 (64.5%) p: Premenopausal: 0.20; Postmenopausal: 0.20 **Adjuvant therapy** 1) n=25: Hormonal and radiotherapy: 17 (68.0%); Chemotherapy and radiotherapy: 5 (20.0%); Radiotherapy alone: 3 (12.0%) 2) n=31: Hormonal and radiotherapy: 21 (67.7%); Chemotherapy and radiotherapy: 9 (29.0%); Radiotherapy alone: 1 (3.3%) p: Hormonal and radiotherapy: 0.62; Chemotherapy and radiotherapy: 0.44; Radiotherapy alone: 0.22

Authors	Intervention	Study Design	Study Population
Rietman, Dijkstra, Geertzen, Baas, de Vries, Dolsma, Groothoff, Eisma & Hoekstra, 2003. **Institution** Departments of Rehabilitation, Surgical Oncology and Radiotherapy, Groningen University Hospital; Northern Centre for Health Care Research, University Groningen; Department of Surgery, Martini Hospital, Groningen, The Netherlands. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: one patient was excluded from the study because she had a prophylactic mastectomy.	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection Radioactive tracer and Patent blue dye (Blue Patenté II; Labatoire Guerbet, Aulnay-sous-Bois, France). Removal of sentinel lymph nodes Not stated Pathology Not stated **2) Axillary clearance (SLNB and/or AC)** Radioactive colloid and/or dye injection Radioactive tracer and Patent blue dye (Blue Patenté II; Labatoire Guerbet, Aulnay-sous-Bois, France). Removal of sentinel lymph nodes/axillary clearance If metastases were identified in the sentinel lymph node, AC was performed within two weeks after SLNB. AC consisted of a Level I/II AC. Pathology Not stated	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Six weeks **Loss to follow-up** Three patients cancelled follow-up appointments before t1 (6 weeks after surgery). One patient was treated elsewhere and the other two found the assessment protocol bothersome and chose to withdraw. **Study Period** June 1999 to June 2001 **Operator Details** Patients retrieved form two hospitals; the Groningen University Hospital had already been using sentinel lymph node biopsy, but the Martini Hospital Groningen introduced sentinel lymph node biopsy halfway during the inclusion period. **Outcome measures** Upper-limb function and activities of daily life were evaluated one day before surgery (t0) and six weeks after surgery (t1). Pain was assessed with a visual analogue scale, patients were asked to mark their current pain perception on a 10cm straight line (0cm = no pain to 10cm = worst pain imaginable). Upper-limb function was assessed during a standardised physical examination. Active shoulder range of motion was measured with a goniometer according to a standardised protocol in forward flexion, abduction and external rotation. The muscle strength of the shoulder abductors and elbow flexors was measured using a hand-held dynamometer (Citec; Groningen, The Netherlands) and grip strength was measured with a Yamar (Bollingbrook, Illinois, USA) hand-dynamometer. All muscle strength measurements were performed three times and the mean of these three measurements was used for further analysis. Upper and forearm circumference was measured with a Gulick measuring tape at 10cm proximal to the olecranon and 15cm proximal to the processus styloideus ulnae. Activities of daily living was assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS). The SDQ contains 16 statements that describe the situations in which patients experience pain and what some of the effects may be, with a three category response format. The total score for the 16 statements ranges from 0 (no functional status limitation) to 100 (maximum functional status limitation). The GARS assesses perceived restrictions (disability) in performing 18 activities of daily living. It has a four category response format. The sum scores range from 18, where the person can perform all activities without any difficulty to 72, where the person cannot perform any activity without the help of others. All objective assessment tools appear to be validated.	**Sample Size** 208 consecutive, 204 after exclusion and losses to follow-up 1) 66 patients 2) 138 patients **Age** Mean 55.6, SD 11.6 years **Type of surgery** 1) n=66 / 2) n=138 Breast conserving: 49 (74.2%) / 70 (50.7%) Modified radical mastectomy: 17 (25.8%) / 68 (49.3%) **Stage of disease** Stage I: 87/208 (41.8%) Stage IIA: 86/208 (41.3%) Stage IIB: 35/208 (16.8%) Stage I (T1N0M0: tumour 2cm or less in greatest dimension [T1], no regional lymph node metastasis [N0], no distant metastasis [M0]) Stage II (T1N1M0, T2N0M0, T2N1M0, T3N0M0; metastasis to movable ipsilateral axillary lymph node [N1], tumour more than 2cm but not more than 5cm in greatest dimension [T2], tumour more than 5cm in greatest dimension [T3]) **Tumour histology** Not stated **Tumour location:** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Schijven, Vingerhoets, Rutten, Nieuwenhuijzen, Roumen, van Bussel & Voogd, 2003. **Institution** Department of Surgery, Catharina Hospital Eindhoven; Section of Clinical Health Psychology, Tilburg University, Tilburg; Department of Surgery, St Joseph Hospital, Veldhoven; Comprehensive Cancer Centre South, Eindhoven Cancer Registry, Eindhoven, The Netherlands. **Inclusion/exclusion criteria** Inclusions: patients who underwent ALND as part of surgical treatment for primary breast cancer within the last three years; were at least three months post-treatment (including radiation and/or adjuvant hormonal or chemotherapy); without signs of active disease. Exclusions: none stated	In order to prevent selection bias, specialists were requested to approach ALND patients consecutively during scheduled follow-up appointments irrespective of the presence of complaints after surgery. SNLB patients were consecutively selected from hospital patient files. **1) Sentinel Lymph Node Biopsy (SLNB)** SLNB procedure was facilitated by administration of 100 Mbq in 0.5 mL of ^{99m}Tc-colloidal-labelled albumin (Nanocoll), peri-tumoural, the day prior to surgery.Static imaging of the axilla using a gamma-camera was done immediately before surgery. Unger general anaesthesia, the patient was injected peri-areolar subdermally with Patent Blue V dye (2.5% solution, Laboratoire Guerbet, Aulnay-sous-Bois, France). The SN was harvested trough a 2-3 cm incision guided by skin surface markings indicative for the visualized SNs on static films and by combined visual/hand-held gamma probe localization. ALND was performed in patients with a positive SN on H&E staining. SLNB patients were not given routine wound drains. SLNB patients were usually discharged one to two days post-operatively. No routine hospital physical therapy was started in the SLNB group. **2) Axillary clearance (AC)** ALND was performed according to established guidelines. ALND patients started physical therapy from day one post-operatively until optimal range was achieved. Most patients were given a drain during surgery in the axillary region, and the drain was usually removed when production was below 40cc/24h. At discharge, patients were instructed by a trained nurse how to resume optimal use of the arm and how to exercise at home. Patients were seen on outpatient basis according to follow-up protocol, starting one week after discharge.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Not stated **Loss to follow-up** Only patients with updated and comprehensive patient records, who filled in the questionnaire completely, were included. This resulted in a reduction of group size. **Study Period** December 1998 to May 1999 (recruitment). **Operator Details** Additional data, such as pTNM classification and post-operative treatment regimen were retrieved from hospital patient files. **Outcome measures** Treatment-specific QOL questionnaire developed and validated by the department of Clinical Health Psychology of Tilburg University, The Netherlands. The questionnaire was pretested and validated (construct and content) in a pilot study (Dons *et al.* 1998).	**Sample Size** 1) 180 (198/248 (79.8%) questionnaires returned) 2) 213 (400/465 (86.0%) questionnaires returned) Note: only patients with updated and comprehensive records, and a fully completed questionnaire were included. **Age** p=0.17 | | 1) n=180 | 2) n=213 | |---|---|---| | < 50 years | 37 (20.6%) | 59 (27.7%) | | 50-65 years | 84 (46.7%) | 116 (54.5%) | | ≥ 65 years | 59 (32.8%) | 38 (17.8%) | **Type of surgery** p=0.00 | | 1) n=180 | 2) n=213 | |---|---|---| | Lumpectomy | 159 (88.3%) | 141 (66.2%) | | Mastectomy | 21 (11.7%) | 72 (33.8%) | **Stage of disease** | | 1) n=180 | 2) n=213 | p | |---|---|---|---| | 0 (DCIS) | 12 (6.7%) | 1 (0.5%) | 0.01 | | I | 105 (58.3%) | 100 (46.9%) | | | II | 61 (33.9%) | 99 (46.5%) | | | III | 2 (1.1%) | 13 (6.1%) | | | IV | 0 (0.0%) | 0 (0.0%) | | | Tis | 12/180 (6.7%) | 1/213 (0.5%) | 0.27 | | T1 (≤ 2cm) | 128/180 (71.1%) | 143/213 (67.1) | | | T2 (> 2cm and ≤ 5 cm) | 38/180 (21.1%) | 58/213 (27.2%) | | | T3 (> 5cm) | 1/180 (0.6%) | 4/213 (1.9%) | | | T4 (tumour invading skin, thorax) | 1/180 (0.6%) | 7/213 (3.3%) | | | N0 (no positive ALN(s)) | 142/180 (78.9%) | 125/213 (58.7%) | 0.00 | | N1 or N2 (metastasis in movable ipsilateral node(s); metastasis in fixed ipsilateral node(s)) | 38/180 (21.1%) | 88/213 (41.3%) | | **Tumour histology** | | 1) n=180 | 2) n=213 | |---|---|---| | Invasive | 168 (93.3%) | 212 (99.5%) | | DCIS | 12 (6.7%) | 1 (0.5%) |

Tumour location
Not stated

Receptor status
Not stated

Menopausal status
Not stated

Adjuvant therapy

	1) n=180	2) n=213	p
Radiotherapy, on axilla	15 (8.3%)	30 (13.9%)	0.01
Radiotherapy, not on axilla	134 (74.4%)	123 (57.7%)	
Chemotherapy	19 (10.6%)	40 (18.8%)	0.02
Hormonal therapy	64 (35.6%)	51 (23.9%)	0.01

Radiation therapy to the axilla and/or supraclavicular region was recommended for patients with inadequate ALND, extracapsular malignant growth at lymph node involvement or nodal involvement in the apex of the axilla. In the SLNB group, patients with a positive SN had radiation therapy recommended according to the pathological outcome of ALND. Patients received post-operative adjuvant hormone or chemotherapy depending on their individual characteristics combined with the results of the pathology, including breast tissue and axillary node histology, mitosis index of the tumour and its oestrogen/progesterone receptor status.

Authors	Intervention	Study Design	Study Population
Schrenk, Rieger, Shamiyeh & Wayand, 2000. **Institution** Second Department of Surgery – Ludwig Boltzmann Institute for Surgical Laparoscopy, Allgemein Offentliches Krankenhaus Linz, Linz, Austria. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB)** Patients with unilateral invasive carcinoma underwent breast surgery and sentinel lymph node mapping. If the sentinel lymph node showed no metastatic disease in intraoperative frozen sections, paraffin section H&E stained or with IHC then no further axillary dissection was performed. Radioactive colloid and/or dye injection Sentinel lymph nodes identified by the injection of patent blue V (2.5% Guerbet®) only (n=17) or dye and Tc99mlabelled radiocolloids (40MBq Tc99m; Nanocoll) (n=18). Removal of sentinel lymph nodes Details not stated although reported elsewhere. The axilla was not drained. Pathology Intraoperative frozen sections (6-8 sections). Paraffin section histology with H&E staining and anticytokeratin staining. **2) Axillary clearance (AC)** Lymph node negative patients that underwent axillary clearance of levels I and II. Patients did not undergo previous sentinel node biopsy because; 1) no sentinel node was found intraoperatively (n=4), 2) palpable (but tumour free) nodes found clinically prior to surgery (n=5), 3) patients did not consent to sentinel node biopsy (n=6), 4) underwent AC for training reasons (n=11), 5) surgeon did not perform sentinel node biopsy (n=8), 6) preoperative lymphscintigraphy showed drainage exclusively to the parasternal lymph nodes (n=1). Dissection was carried out below the axillary vein without skeletonizing the vein. The long thoracic nerve and the thoracodorsal nerve and vessels were preserved and the intercostobrachial nerve was preserved where possible. The axilla was drained after clearance, and drain was removed when the amount of daily drainage was <30cc. Pathology Not stated	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** p=0.0236 1) mean 15.4 ± 6.2, range 4 to 28 months 2) mean 17.0 ± 5.6, range 4 to 28 months **Loss to follow-up** Not stated **Study Period** December 1996 to December 1998 **Operator Details** Not stated **Outcome measures** Follow-up examinations were performed every three months after surgery; The following measurements were recorded: *arm swelling* was noted 15cm above and 10cm below the lateral epicondyle (mean of 3 measurements), measurements taken of both arms prior to surgery and during postoperative follow-up; *oedema* was assessed subjectively by asking the patient to compare swelling of the operated arm with the nonoperated arm; *numbness* was assessed comparing sensitivities of inner and outer skin areas of the upper arm, axilla and chest wall with the nonoperated side – recorded as numbness or no numbness; *pain* in the operated arm was evaluated using a Visual Analoge Scale (VAS) ranging from 0 (no pain) to 10 (worst pain imaginable); *shoulder joint and arm mobility* was assessed by asking the patient to elevate the operated arm over her head to the other shoulder, to move the arm back and forth, to move the arm behind the back to reach the other scapula and to perform internal and external arm rotation, motion restriction was noted using a scale of 0 (no restriction) to 3 (severe restriction); *arm* strength was measured when both arms were elevated to 90° and then asking the patient to elevate further against pressure applied by surgeon, strength was rated from 0, the same strength in both arms, to 3, operated arm feeble; *stiffness* of the operated arm was assessed as either stiffness or no stiffness; patients were asked whether the surgery affected their *daily living* (yes/no answer). Scales for subjective assessment of arm oedema, arm mobility and arm strength are neither validated nor referenced.	**Sample Size** 1) 35 patients 2) 35 patients **Age** p=NS 1) 62.7 ± 10.4 (SD), range 39 to 76 2) 58.9 ± 12.7 (SD), range 33 to 77 **Type of surgery** p=NS 1) n=35: Quadrantectomy 27 (77%), Mastectomy 8 (23%) 2) n=35: Quadrantectomy 26 (74%), Mastectomy 9 (26%) **Stage of disease** T1a: 1) 1 (2.9%), 2) 0 (0.0%), p - T1b: 1) 8 (22.9%), 2) 6 (17.1%), p=NS T1c: 1) 19 (54.3%), 2) 20 (57.1%), p - T2: 1) 7 (20.0%), 2) 9 (25.7%), p - **Tumour histology** Not stated **Tumour location** p=NS Right breast: 1) 22 (62.9%), 2) 21 (60.0%) Left breast: 1) 13 (37.1%), 2) 14 (40.0%) **Receptor status** Not stated **Menopausal status** p=NS Premenopausal: 1) 5 (14.3%), 2) 7 (20.0%) Postmenopausal: 1) 30 (85.7%), 2) 28 (80.0%) **Adjuvant therapy** p=NS Radiation: 1) 24/35 (68.5%), 2) 25/35 (71%) Chemotherapy: 1) 7/35 (20.0%), 2) 7/35 (20.0%) Hormonal: 1) 28/35 (80.0%), 2) 28/35 (80.0%) Radiation: 45Gy to the breast over 5 weeks with a boost to the tumour bed, the axilla was excluded from the radiation field. Hormonal: Tamoxifen

Authors	Intervention	Study Design	Study Population
Sener, Winchester, Martz, Feldman, Cavanaugh, Winchester, Weigel, Bonnefoi, Kirby & Morehead, 2001. **Institution** Departments of Surgery and Medicine, Evanston Northwestern Healthcare, Evanston, IL, USA; Departments of Surgery and Medicine, Northwestern University Medical School, Chicago, IL, USA. **Inclusion/exclusion criteria** Inclusions: consecutive patients with invasive carcinoma. Exclusions: none stated	**1) Sentinel Lymph Node Biopsy (SLNB)** Radioactive colloid and/or dye injection All patients received1mCi filtered (0.22 micrometre filter) ^{99m}Tc-labelled sulphur colloid, diluted to 8cc and injected in a 4 quadrant distribution peritumorally. All patients had preoperative lymphoscintigraphy. Time between injection and excision ranged from 16-20 hours. Patients with nonpalpable tumours underwent wire localization before injection. Removal of sentinel lymph nodes Sentinel nodes were identified intraoperatively, transcutaneously using a hand-held gamma probe. Radiolabelled nodes were examined off the operative field, and if the ex vivo radioactivity was at least three times the lymph node basin background level, the node was considered to be a sentinel node. Pathology Details not stated. **2) Axillary clearance (SLNB +AC)** During the validation phase (phase I) of the study, 72 patients underwent sentinel lymph node biopsy followed by level I-II axillary clearance. Subsequent to phase I, phase II commenced where only patients who had a positive sentinel node under went level I-II axillary clearance. Pathology Details not stated.	Non-randomised comparative study **Level of Evidence** Level III-2 **Follow-up** Median follow-up for entire cohort 24 months, for patients who underwent SLNB alone 19 months **Loss to follow-up** Not stated **Study Period** December 1996 to April 2000 **Operator Details** Not stated **Outcome measures** Lymphoedema measurements were collected at the beginning of the second phase (where AC was only performed if sentinel node was positive for metastases) including; arm measurement obtained preoperatively and at intervals during follow-up. Severity of lymphoedema was classified according to a modification of original definitions of Stillwell *et al.* (1969).[110] Postoperative volume differences <20% between arms were defined as mild, 21-40% moderate, >40% severe.	**Sample Size** 1) 303 patients 2) 117 patients **Age** Not stated **Type of surgery** Lumpectomy or mastectomy, proportions not stated. **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** 1) n=303 / 2) n=117 Upper outer: 155 (51.2%) / 62 (53.0%) Other location: 148 (48.8%) / 55 (47.0%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Radiation*:* for patients who had lumpectomy, 5040cGy was delivered to the remaining breast in 33 fractions, and an additional 1000cGy was used to boost the lumpectomy site. With the exception of 1 patient, no attempt was made to include the axilla in the radiation port.

<table>
<tr><th>Authors</th><th>Intervention</th><th>Study Design</th><th>Study Population</th></tr>
<tr>
<td>Swenson, Nissen, Ceronsky, Swenson, Lee & Tuttle.

Institution
Park Nicollet Institute, Minneapolis, MN, USA; The Breast Center of United Hospital, St Paul, MN, USA; The University of Minnesota, Division of Surgical Oncology, Minneapolis, MN, USA.

Inclusion/exclusion criteria
<u>Inclusions</u>: consecutive patients with clinical stage 0 to II breast cancer; planned SLNB or SLNB + AC; agreed to participate and signed a consent form. <u>Exclusions</u>: patients who had prior chemotherapy for breast cancer; multicentric breast cancer; prior extensive breast or axillary surgery; unable to read or write English.</td>
<td>1) Sentinel Lymph Node Biopsy (SLNB)

<u>Radioactive colloid and/or dye injection</u>
Identification by technetium-labelled sulphur colloid and isosulfan blue dye.

<u>Removal of sentinel lymph nodes</u>
Not stated

<u>Pathology</u>
Intraoperative frozen section was performed on SLNs. Routine H&E and IHC was also performed.

2) Axillary clearance (SLNB and/or AC)
A routine level I/II AC was performed if metastases were identified in the SLN (56/247 (23%) patients), or if no SLN was identified (11/247 (4.5%) patients) or if the surgeon was in the process of SLNB training (11/247 (4.5%) patients).

<u>Pathology</u>
Nodes from AC were examined for metastases using routine H&E.</td>
<td>Non-randomised comparative study

Level of Evidence
Level III-2

Follow-up
1, 3 and 12 months

Loss to follow-up
247/261 (95%) of identified patients completed at least one survey (and were included in the analysis); 232/261 (88%) completed the 1 month survey; 225/261 (86%) completed the 6 month survey; 211/261 (68%) completed the 12 month survey.

Study Period
February 1999 to November 2000.

Operator Details
Surgeons from both institutions (Park Nicollet Health Services and The Breast Center of United Hospital) attended a training course in SLNB.

Outcome measures
Measure of Arm Symptom Survey (MASS) was developed for this study as there were no instruments available to comprehensively assess arem symptoms. The MASS assessed breast, chest and axillary pain; numbness or tingling of the breast, chest axilla or arm; limitation of shoulder or arm range of motion; arm or hand swelling; symptom severity and degree of interference with life activities for each symptom. Face validity was established, reliability testing was not performed. MASS was administered to all participants at 1, 6 and 12 months. Paticipants who did not respond were sent a reminder with another copy of the questionnaire.</td>
<td>Sample Size
1)169
2) 78

Age
1) mean 57.9 , median 57, range 28 to 87 years
2) mean 54.2, median 53, range 37 to 79 years

Type of surgery
<table>
<tr><td></td><td>1) n=169</td><td>2) n=78</td></tr>
<tr><td>Breast conserving</td><td>141 (83.4%)</td><td>43 (55.1%)</td></tr>
<tr><td>Mastectomy</td><td>18 (10.7%)</td><td>29 (37.2%)</td></tr>
<tr><td>Mastectomy with reconstruction</td><td>10 (5.9%)</td><td>6 (7.7%)</td></tr>
</table>
Stage of disease
Tumour size: mean 1.7cm
<table>
<tr><td></td><td>1) n=169</td><td>2) n=78</td></tr>
<tr><td><2.0cm</td><td>132 (78.1%)</td><td>44 (56.4%)</td></tr>
<tr><td>>2.0cm</td><td>35 (20.7%)</td><td>33 (42.3%)</td></tr>
<tr><td>Stage 0</td><td>5 (3.0%)</td><td>0 (0.0%)</td></tr>
<tr><td>Stage I</td><td>116 (68.6%)</td><td>19 (24.4%)</td></tr>
<tr><td>Stage II</td><td>46 (27.2%)</td><td>52 (66.7%)</td></tr>
<tr><td>Stage III</td><td>1 (0.6%)</td><td>6 (7.7%)</td></tr>
</table>
Tumour histology
Not stated

Tumour location
Not stated

Receptor status
Not stated

Menopausal status
Not stated

Adjuvant therapy
Radiotherapy to the axilla was not performed.
<table>
<tr><td></td><td>1) n=169</td><td>2) n=78</td></tr>
<tr><td>Chemotherapy</td><td>67 (39.6%)</td><td>67 (85.9%)</td></tr>
<tr><td>Radiotherapy</td><td>132 (78.1%)</td><td>51 (65.4%)</td></tr>
<tr><td>Hormonal therapy</td><td>119 (70.4%)</td><td>56 (71.8%)</td></tr>
</table>
</td>
</tr>
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Authors	Intervention	Study Design	Study Population
Temple, Baron, Cody, Fey, Thaler, Borgen, Heerdt, Montgomery, Petrek & Van Zee, 2002. **Institution** Department of Surgery, Breast Service and Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. **Inclusion/exclusions criteria** Inclusions: patients undergoing breast-conserving therapy with SLNB or breast-conserving therapy with SLNB followed by immediate or delayed AC. Exclusions: patients <18 years of age, surgery for prior breast cancer, bilateral breast surgery, preoperative chemotherapy. Note: same patients but longer follow-up but presented in addition to Baron *et al.* 2002.	**1) Sentinel Lymph Node Biopsy (SLNB)** No details given **2) Axillary clearance (SLNB + AC)** No details given	Non-randomised comparative study **Level of Evidence:** Level III-2 **Follow-up:** 12 months **Loss to follow-up** Only patients who completed the BSAS at all time points (baseline, 3,6, and 12 months) were included in formal analysis **Study Period** November 1 1999 and November 1 2000 **Operator Detail** Research assistant recruited patients at initial postoperative visit (3-15 days postop.) and made reminder calls if mailed follow-up questionnaires were not returned. **Outcome measures** Memorial Sloan-Kettering Cancer Center Breast Sensation Assessment Scale (BSAS©) was completed at the initial postoperative visit and mailed to patients at 2, 5 and 10 months following their surgery. The BSAS© has been demonstrated to have good internal consistency, test-retest reliability and validity. Lymphoedema was measured by arm measurementst taken at the time of surgery and 12 months postop. Both arms were measured at 10cm above and 5cm below the olecranon process.	**Sample Size** 1) 171 2) 62 **Age** 1) median 59, range 27 to 84 years 2) median 54, range 33 to 77 years **Type of surgery** Breast-conserving therapy, proportions not stated. **Stage of disease** 1) n=171 / 2) n=62 Invasive tumour size: 1.2, SD 0.63 (n=157 – available data) / 1.8cm, SD 0.83 Stage I: 148 (86.5%) / 3 (4.8%) Stage II: 15 (8.8%) / 59 (95.2%) **Tumour histology** 1) n=171 / 2) n=62 Invasive carcinoma: 163 (95.3%) / 62 (100%) DCIS: 8 (4.7%) / 0 (0.0%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** 1) n=171 / 2) n=62 Radiation: 98 (57.3%) / 7 (11.3%) Chemotherapy: 0 (0.0%) / 0 (0.0%) Radiation and Chemotherapy: 65 (38.0%) / 53 (85.5%) No adjuvant therapy: 8 (4.7%) / 2 (3.2%)

Table I.3 Case series – Safety and Efficacy

Authors	Intervention	Study Design	Study Population
Acosta, Contreras, Ravelo, Hurtado, Marín, Manso, Pérez & Longobardi, 2003. **Institution** Centro Clinico de Estereotaxia, Caracas, Venezuela, South America. **Inclusion/exclusion criteria** Inclusions: breast cancer patients with a tumour size of ≤2cm, determined by clinical examination, mammography and ultrasound in the case of infiltrating tumours, and larger than 4cm in cases of DCIS (extensive ductal carcinoma), and a clinically negative axilla. Exclusions: patients with multiple local lesions, pregnant women and male patients were excluded.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Peritumoral injection of dye (isosulfan blue or patent blue) was used, with an average dose of 2.5cc, injected 10 minutes before carrying out the axillary incision. In 51/57 (89.5%) of cases, dye was combined with a peritumoral injection of nonfiltered ^{99m}Tc-labelled colloidal sulphide, with an average dose of 1μCi. The radiocolloid was injected 4 to 18 hours (average 12 hours) prior to the surgical procedure. Lymphoscintigraphy was not performed. Removal of sentinel lymph nodes A hand-held gamma probe (Europrobe; Eurorad, Strasbourg, France) was used to locate the most radioactive point in the axilla, and an incision, approximately 3cm was made in the line of the insert of the axillary hair. Dissection was performed carefully, in layers, using the gamma probe as a guide, and the blue stain as a visual guide, until the nodal structure was identified. The in vivo radioactivity was determined and the node was excised. The ex vivo radioactivity count was verified. After the node was removed, the axilla was explored using the gamma probe to rule out the presence of further sentinel nodes. Pathology All cases were evaluated by the same pathologist, and when the sample allowed, histologic cuts were performed and cytology was used as a support for the H&E frozen sectioning.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** February 1998 to August 2001 **Operator details** All cases reviewed by the same pathologist. **Outcome measures** Not applicable	**Sample size** 57 patients **Age** Mean 52, range 32 to 73 years **Type of surgery** Mastectomy 57/57 (100%) **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Albo, Wayne, Hunt, Rahlfs, Singletary, Ames, Feig, Ross & Kuerer, 2001. **Institution** Department of Surgical Oncology; Department of Anesthesiology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Preoperative lymphoscintigraphy was performed in all patients. ^{99m}Tc-labelled sulfur colloid was injected around the tumour site or biopsy cavity at a dose of either 0.5mCi (1-4 hours before surgery) or (2.5 mCi (24 hours before surgery). After induction of general anaesthesia, 3-5cc of isosulfan blue (Lymphzurin 1%; US Surgical Corporation, Norwalk, CT, USA) was injected around the tumour or biopsy cavity. The area of injection was massaged for 5 min. Removal of sentinel lymph nodes A hand held gamma probe was used to identify the area of maximum radioactivity in the axilla. A 2-4cm incision was made at this site. The dissection was carried through the subcutaneous fat and axillary facia in order to identify the blue-stained lymphatic channels in their course toward the SLNs. The hand held gamma probe was used intraoperatively to localize the SLNs. Any node that was blue or at least 10 times greater than the background counts in the axilla was considered a SLN. After removal of the SLNs the operative area was checked with the probe to ensure low axillary background counts. Further dissection was performed if axillary counts remained high. Pathology During surgery, a pathologist examined the sentinel nodes using touch preparation cytology. Patients in whom the intraoperative analysis determined that the SLNs harbored malignant cells underwent completion AC.	Case series **Level of evidence** Level IV **Follow-up** Not stated and not applicable **Loss to follow-up** Not stated and not applicable **Study period** January 1997 to September 2000 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 639 patients **Age** Not stated (individual cases given in table) **Type of surgery** Segmental or total mastectomy as indicated, proportions not stated. **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Altinyollar, Kapucuoglu, Pak & Berberoglu, 2000. **Institution** Department of General Surgery; Department of Pathology, Ankara Onkoloji Hospital, Ankara, Turkey. **Inclusion/exclusion criteria** Inclusions: none stated. Exclusions: pregnant women.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Under general anaesthesia, 4ml of patent blue dye (2.5% solution in distilled water prepared by adding 0.6% sodium chloride and 0.05% disodium hydrogen phosphate) was injected interparenchymally at four quadrants (1ml per quadrant) around the biopsy cavity (tumours were excised before modified radical mastectomy). Injection sites were gently massaged for 2 to 3 minutes. Removal of sentinel lymph nodes Five minutes after injection, the axillary part of the transverse incision of mastectomy was incised 5 to 6cm below the hairline. Stained lymphatic vessels were followed by sharp dissection and the blue stained lymph node was searched for. Pathology Lymph nodes were evaluated by frozen section on H&E slides. SNs were also stained with an anti-cytokeratin antibody (1:50, clone: AE1/AE3, Neomarkers, USA). A level I/II/III axillary was carried out as part of the modified radical mastectomy in all cases.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 60 patients **Age** Median 51, range 31 to 74 years **Type of surgery** Modified radical mastectomy **Stage of disease** Clinical stage I and II T1 (<2cm) 19/60 (31.7%) T2 (2 to 5cm) 41/60 (68.3%) **Tumour histology** Invasive ductal carcinoma 51/60 (85%) Invasive lobular carcinoma 4/60 (6.7%) Atypical medullary carcinoma 3/60 (5%) Mucinous carcinoma 2/60 (3.3%) **Tumour location** UOQ 46/60 (76.7%) UIQ 4/60 (6.7%) LOQ 5/60 (8.3%) LIQ 2/60 (3.3%) Subareolar 3/60 (5%) **Receptor status** Oestrogen receptor positive 18/60 (30.0%) Oestrogen receptor negative 42/60 (70.0%) **Menopausal status** Premenopausal 22/60 (36.7%) Postmenopausal 38/60 (63.3%) **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Balch, Mithani, Richards, Beauchamp & Kelley, 2003. **Institution** Division of Surgical Oncology, Vanderbilt University Medical Center, Nashville, Tennessee, USA. **Inclusion/exclusion criteria** Inclusions: all patients undergoing definitive surgical treatment were eligible to participate in a prospective clinical trial, initiated in July 1997. Initially, all patients undergoing lymphatic mapping and sentinel lymph node biopsy were entered into the protocol, and by August 1 1999, 90 women had participated and it was determined that all participating surgeons had achieved the desired benchmarks of >95% identification rate, <5% false negative rate. Lymphatic mapping with sentinel lymph node biopsy without routine axillary clearance was performed on patients with early-stage disease (<3cm primary tumour and clinically node negative). The protocol remained open and continued to accrue patients who did not meet these criteria and/or had undergone preoperative therapy, and also patients were accrued from surgeons who had not met the credentialing benchmarks, to perform sentinel lymph node biopsy without axillary clearance. Of the 122 patients entered into the study, 50 (40.9%) had stage II or III disease (American Joint Committee on Cancer TMN system). Diagnosis was established by fine needle aspiration, core needle biopsy, or incision or excisional biopsy. Fine needle aspiration was perfomed on patients with clinically positive axillary nodes, and clinical staging was assigned on the bases of these evaluations. Of these patients 32/50 (64.0%) had received neoadjuvant therapy and are the subjects of this study. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection A total of 450μCi of filtered 99mTc-sulfur colloid was injected peritumorally, 2 to 6 hours before surgery. The last 26 patients (of the 32 who received neoadjuvant therapy) also received 300μCi of filtered sulphur colloid intradermally over the primary lesion. Lymphoscintigraphy was performed in most patients. After induction of anaesthesia, 5ml of 1% isosulfan blue was injected peritumorally and the breast was massaged for 5 minutes. Removal of sentinel lymph nodes An axillary incision was made and the axilla was bluntly dissected to identify blue stained lymphatics or nodes. A hand-held gamma probe (Navigator; US Surgical Corp., Norwalk, CT, USA) was used to localise radioactive nodes. All blue or significantly radioactive (≥5 times the background in the nodal basin and/or ≥30 counts *in vivo*) nodes were excised and labelled as sentinel nodes. If radioactivity ≥30 counts remained in the axilla after the excision of the sentinel node, dissection continued to find any additional sentinel nodes. Palpable or clinically suspicious nodes were also removed, but labelled as non-sentinel unless blue and/or radioactive. Pathology Sentinel nodes were evaluated with 1mm serial sections and stained with H&E. Immunohistochemical staining with a monoclonal anticytokeratin antibody cocktail (AE1/AE3; Dako Corp., Carpinteria, CA, USA) was used selectively at the pathologist's discretion to clarify questionable areas identified by H&E. Nonsentinel nodes were evaluated with standard processing and H&E. All patients underwent sentinel lymph node biopsy followed by axillary clearance (level I and II).	Case series **Level of evidence** Level IV **Follow-up** Patients were evaluated every 3 to 4 months with physical examinations and yearly with mammography and laboratory or radiological studies as indicated on the basis of symptoms or findings of physical examination. Median 24, range 9 to 62 months **Loss to follow-up** 28/32 (87.5%) alive at follow-up **Study period** July 1997 to February 2002 **Operator details** Not stated **Outcome measures** Local, regional and systemic recurrence and survival were prospectively evaluated.	**Sample size** 32 cases **Age** Mean 51, range 28 to 75 years **Type of surgery** Total mastectomy: 17/32 (53.1%) Segmental mastectomy: 15/32 (46.9%) **Stage of disease** Stage IIa: 8/32 (25.0%) Stage IIb: 9/32 (28.1%) Stage IIIa: 8/32 (25.0%) Stage IIIb: 7/32 (21.9%) **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Neoadjuvant therapy** 25/32 (78.1%) received doxorubicin-based chemotherapy off protocol, 12/25 (48.0%) 5-fluorouracil, cyclophosphamide and doxorubicin (FAC) and 13/25 (52.0%) doxorubicin and cyclophosphamide (AC) and 7/32 (21.9%) received paclitaxel (175mg/m^2 intravenously every 3 weeks for 3 cycles, followed by concurrent paclitaxel (60mg/m^2 intravenously twice weekly for 6 weeks) and radiotherapy (46.8Gy over 6 weeks to the whole breast and supraclavicular fossa). Pathologic response to preoperative therapy Complete: 2/32 (6.3%) Major partial: 25/32 (78.1%) Minor partial: 3/32 (9.4%) Stable: 2/32 6.3%) Downstaged: 22/32 (68.8%) **Adjuvant therapy** In general, most patients who received preoperative FAC or AC received four cycles of paclitaxel followed by breast or chest wall radiotherapy. Patients who participated in the trial

			that evaluated preoperative paclitaxel received four cycles of AC after surgery. All women with hormonal receptor-positive tumours received tamoxifen (20mg) daily, orally for five years.

Authors	Intervention	Study Design	Study Population
Blessing, Stolier, Teng, Bolton & Fuhrman, 2002. **Institution** Department of Surgery, Ochsner Clinic Foundation, New Orleans, Louisiana, USA. **Inclusion/exclusion criteria** Inclusions: all patients with clinically negative axillae with T1 and T2 breast cancer. Exclusions: investigators do not rely on sentinel lymph node mapping in patients treated with neoadjuvant chemotherapy, or who have received prior radiotherapy.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The technique of colloid injection varied among the four surgeons in the institution. One surgeon favoured a four-injection peritumoral technique, while the others use a 1cc subcutaneous injection directly overlying the tumour. Lymphoscintigraphy was not performed. The technique of dye injection was the same is all cases, where dye is injected after intravenous sedation or general anaesthesia is achieved. A volume of 3 to 5cc of dye is used and is injected peritumorally. The volume injected is based on the distance from the primary tumour to the axilla. A five minute massage of the breast follows the injection. From April1 2001 to August 15 2001 all patients were evaluated with isosulphan blue dye (lymphazurin), from August 15 2001 to December 17 2001 all patients were evaluated with methylene blue as isosulphan blue was not available. For the final 3.5 months of the study, the choice of dye was left to the surgeons discretion. Removal of sentinel lymph nodes Success was defined as the ability to identify at least one sentinel node based on either dye or radiocolloid. The definition of a hot node was a node that had a gamma probe count that is ten times the background count in the axilla or 10% of the count of the most radioactive node. A node was defined as sentinel if it countains blue dye or has a blue-stained lymphatic leading to it. Pathology Lymph nodes less than 0.5cm were completely embedded, 0.5 to 1cm were halved, >1cm were cut into ± 0.5cm slices. Blue and/or radioactive nodes were subject to H&E and additional (five level) skip sectioning and immunohistochemical staining using CAM 5.2 (Becton-Dickinson, San José, CA, USA). Nonsentinel nodes were subject to H&E only. Intraoperative frozen section analysis of the sentinel nodes was required when sentinel lymph node biopsy was introduced as standard protocol. The initial study design required sentinel lymph node biopsy to be followed by axillary clearance but sing November 1997, sentinel lymph node biopsy has become standard protocol in this institution and axillary clearance is now performed selectively if sentinel lymph biopsy fails, if there are metastases or any doubt concerning the reliability of the procedure.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** April 1 2001 to March 31 2002 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** Group 1: 87 patients Group 2: 112 patients **Age** Group 1: 61.2 years Group 2: 57.7 years (No significant differences between groups, p>0.05). **Type of surgery** Not stated **Stage of disease** T1 or T2 **Tumour histology** Group 1: intraductal 8/87 (9.2%) Group 2: intraductal 7/112 (6.3%) (No significant differences between groups, p>0.05). **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Borgstein, Meijer, Pijpers & van Diest, 2000. **Institution** Departments of Surgical Oncology, Nuclear Medicine and Pathology, Academic Hospital of the Vrije Universiteit, Amsterdam, The Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients with clinical stage T1-T2, N0 breast cancer were eligible after informed consent was obtained. Exclusions: patients with palpable axillary nodes, tumours >5cm, multifocal disease, prior radiation therapy, or extensive surgery to the breast or axilla, or pregnant women.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection A dose of 40 to 60MBq of 99mTc-labelled colloidal albumin (Nanocoll; Sorin Biomedica, Sallugia, Italy) in 4ml of saline was injected peritumorally in 2 to 4 depots around the primary tumour, guided by palpation or adjacent to the biopsy scar, injection was guided by stereotaxy or ultrasound with nonpalpable lesions. Lymphoscintigraphy was performed both 2 and 18 hours after injection. After induction of general anaesthesia, 0.5 to 1ml of Patent Blue V dye (2.5% solution; Laboratoire Guebet, Aulnay-sous-Bois, France) was injected intradermally. In the initial set of patients (group 1), the injection was placed into the skin directly overlying the tumour site. In a consecutive group of patients (group 2), the intracutaneous injection was placed along the lateral border of the areola, irrespective of breast tumour location. The injection site was gently massaged for 5 minutes. Removal of sentinel lymph nodes A 3 to 5cm axillary incision was made in the standard location for axillary clearance or the predetermined line for mastectomy. Careful dissection was performed using guidance of audio signals from the hand-held gamma probe (C-track; Care Wise, Morgan Hill, CA, USA). Whenever possible, all blue lymphatic ducts were pursued to the first draining node/s. In order of their discovery, all blue nodes were removed and the *ex vivo* count recorded. Lymph nodes with the most tracer uptake were defined as true sentinel nodes, whereas those with less than 50% of the highest count rate were considered to be secondary nodes. Pathology Lymph nodes less than 0.5cm were completely embedded, 0.5 to 1cm were halved, >1cm were cut into ± 0.5cm slices. Blue and/or radioactive nodes were subject to H&E and additional (five level) skip sectioning and immunohistochemical staining using CAM 5.2 (Becton-Dickinson, San José, CA, USA). Nonsentinel nodes were subject to H&E only. Intraoperative frozen section analysis of the sentinel nodes was required when sentinel lymph node biopsy was introduced as standard protocol. The initial study design required sentinel lymph node biopsy to be followed by axillary clearance but sing November 1997, sentinel lymph node biopsy has become standard protocol in this institution and axillary clearance is now performed selectively if sentinel lymph biopsy fails, if there are metastases or any doubt concerning the reliability of the procedure.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** September 1996 to April 1999 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 217 patients (216 female:1 male); 220 cases (3 bilateral tumours) **Age** Mean 57 ± 12, range 31 to 87 years **Type of surgery** Lumpectomy 170/220 (77.3%) Mastectomy 50/220 (22.7%) **Stage of disease** Mean 1.9 ± (SD) 1.0cm (pathological size) <1cm (T1a-b) 40/208 (19.2%) 1 to 2cm (T1c) 102/208 (49.0%) >2cm (T2) 66/208 (31.7%) Note: results for invasive cancers, 4/220 (1.8%) cases were benign and 8/220 (3.6%) were pure DCIS. **Tumour histology** Benign 4/220 (1.8%) DCIS 8/220 (3.6%) Ductal 164/220 (74.5%) (2 cases were DCIS with microinvasion) Lobular 22/220 (10.0%) Other 22/220 (10.0%) **Tumour location** UOQ 114/220 (51.8%) UIQ 31/220 (14.1%) LOQ 35/220 (15.9%) LIQ 13/220 (5.9%) Central 27/220 (12.3%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Carcoforo, Basaglia, Soliani, Bergossi, Corcione, Pozza & Feggi, 2002. **Institution** Dipartimento di Scienze Chirurgiche, Radiologiche ed Anestesiologiche, Sezione di Clinica Chirurgica, Universitá di Ferrara, UO di Radiologia, Azienda Ospedaliera Arcispedale S Anna, Ferrara, UO di Medicina Nuclare, Azienda Ospedaliera Arcispedale S Anna, Ferrara, Italy. **Inclusion/exclusion criteria** Inclusions: patients had mammographic or ultrasonographic evidence of T1 breast cancer with histological confirmation; axilla was clinically negative. Exclusions: not stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection A nanocolloidal tracer labelled with Tc 99m (Nanocoll®, Nycomed Amersham Sorin, Saluggia, Italy) with average particle size <80 nm was injected the afternoon before surgery. An average dose of 130MBq (range 110-150) was injected peritumorally to have 10 MBq of radioactivity at time of surgery. The administered volume was 0.3-0.4 cc and was performed under touch control for patients with palpable breast lesions. Sonographic or stereographic guidance was used for non-palpable lesions. Scintigraphy was performed the morning of surgery, about 17 hr after tracer administration, using a large-field-of-view gamma camera. Removal of sentinel lymph nodes A gamma probe (Scintiprobe mr 100®) with lymphoscintigraphic imaging was used intraoperatively to locate sentinel nodes and to guide its surgical removal. Pathology Histological examination after embedding in paraffin was usually requested, and multilevel sectioning of the SN was performed with H&E staining and IHC.	Case series **Level of evidence** Level IV **Follow-up** Not stated. **Loss to follow-up** Not stated. **Study period** November 1997 to June 2001 **Operator details** Not stated. **Outcome measures** Not applicable.	**Sample size** 143 patients **Age** Median 61, range 43 to 80 years **Type of surgery** Conservative surgery 130/143 (90.9%) (13/143 (9.1%) patients had central tumours and therefore did not have conservative surgery). **Stage of disease** Not stated **Tumour histology** Infiltrating carcinoma **Tumour location** UOQ 5/27 (18.5%) UIQ 6/27 (22.2%) LOQ 12/27 (44.4%) LIQ 4/27 (14.8%) Central 13/143 (9.1%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Choi, Barsky & Chang, 2003. **Institution** Departments of Surgery and Pathology, Revlon/UCLA Breast Center, UCLA Medical Center, Los Angeles, California, USA. **Inclusion/exclusion criteria** Inclusions: consecutive patients with unicentric, histologically proven and clinically small (mainly T1) breast cancers and negative axillary examination. Exclusions: not stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Unfiltered 99mTc-labelled sulphur colloid (1 to 2mCi in 8ml) was injected intramammary in four divided doses around the tumour or biopsy cavity. For non palpable breast cancers, 1mCi wus injected after the placement of a wire for tumour localisation. For patients with either palpable or previously excised lesions, 2mCi was given on the day before surgery. For non palpable lesions, the radiocolloid was injected on the day of surgery, but a minimum of 2.5 hours was given between injection and surgery. Lymphoscintigraphy was performed. Blue dye (3 to 8ml) was injected in a similar manner to the radiocolloid. Removal of sentinel lymph nodes A hand-held gamma probe (C-trak; Care Wise Medical, Morgan Hill, CA, USA) was used to count the radioactivity. In the axilla, the area with the highest radioactivity was marked to guide incision. Pathology All sentinel nodes were examined by H&E and cytokeratin immunohistochemistruy.	Case series **Level of evidence** Level IV **Follow-up** 12, range 5 to 24 months **Loss to follow-up** Not applicable **Study period** September 1998 to May 2000 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 81 patients (83 mapping procedures, 2 patients with bilateral breast cancer) **Age** Mean 56.2 ±(SD) 12.2, range 26 to 81 years 20 to 29 years: 2/81 (2.5%) 30 to 39 years: 5/81 (6.2%) 40 to 49 years: 17/81 (21.0%) 50 to 59 years: 30/81 (37.0%) 60 to 69 years: 13/81 (16.0%) 70 to 79 years: 11/81 (13.6%) 80 to 89 years: 3/81 (3.7%) **Type of surgery** Lumpectomy: 77/83 (92.8%) Mastectomy: 6/83 (7.2%) **Stage of disease** Mean 1.55 ± (SD) 1.31cm Tis: 1/83 (1.2%) T1a (≤0.5cm): 7/83 (8.4%) T1b (0.6-1.0cm): 19/83 (22.9%) T1c (1.1-2.0cm): 44/83 (53.0%) T2: 11/83 (13.3%) T3: 1/83 (1.2%) **Tumour histology** Not stated **Tumour location** Right: 44/81 (54.3%) Left: 35/81 (43.2%) Bilateral: 2/81 (2.5%) UOQ: 51/83 (61.4%) UIQ: 15/83 (18.1%) LOQ: 7/83 (8.4%) LIQ: 8/83 (9.6%) Central: 1/83 (1.2%) UIQ + LIQ: 1/83 (1.2%) **Receptor status** Not stated **Menopausal status**

			Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Cox, Salud & Harrinton, 2000. **Institution** H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa, Florida, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Lymphazurin 1% (isosulfan blue) utilised. Intraparenchymal injection of 5 cc of blue dye, injected in multiple sites around the tumour or excisional biopy site, is the preferred method of isosulfan blue injection. The dye may be injected through a 27-guage needle and fanned through a single injection site or multiple injection sites into the upper, outer (axillary) aspect of the tumour or biopsy site. Following injection, manual compression of the breast and gentle massage for five continuous minutes is performed just prior to skin preparation and draping for surgery. Removal of sentinel lymph nodes SN is localised by making an incision approximately 1 cm inferior to the hairline of the axilla. Dissection may proceed quickly to the clavi-pectoral fascia, after which care is taken to avoid damage to any lymphatic channels beyond this point. Disruption of the lymphatic channels at this level will seriously hinder the ability to find a SN. Superficial channels may lead to the SN, however deeper channels are more likely to carry most of the blue dye to the SN. Pathology Not stated/applicable	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** Over 1700 patients **Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Classe, Curte, Campion, Rousseau, Fiche, Sagan, Resche, Pious, Andrieux & Dravet, 2003. **Institution** Service de Chirurgie Oncologique, Centre René Gauducheau, Site Hôpital Nord; Institute National de Santé et de Recherche Médicale; Service de Biostatistique et DIM; Service de Médecine Nucléaire, Centre René Gauducheau; Service d'Anatomie Pathologique Centre Hospitalier Universitaire, Site Hôpital Nord, Nantes, France. **Inclusion/exclusion criteria** Inclusions: preoperative diagnosis (cytopuncture or microbiopsy) of invasive carcinoma, and indication for conservative surgical treatment (T0, T1, T2), clinically negative axillary lymph nodes (N0) and signed consent. Exclusions: pregnancy, palpable suspicious axillary lymph nodes (N1, N2), neoadjuvant treatment (including surgery, neoadjuvant chemotherapy), and indication for radical surgical treatment and refusal by the patient to give informed consent.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Unfiltered ^{99m}Tc-labelled rhenium sulphate colloid was injected intraparenchymally as two 0.1ml injections towards the axillary ends of the tumour. Activity of 0.8mCi (29.6MBq) was given if the injection was performed on the day before surgery and 0.5mCi (18.5MBq) when the injection was performed on the morning of the procedure. Lymphscintigraphy was performed 2 hours after injection and the day after. Patent Blue dye was injected peritumorally, and intraparenchymally in two injections of 1ml after the induction of general anaesthesia. Removal of sentinel lymph nodes Intraoperative detection was performed using a hand-held gamma probe (Modelo 2^{R}; DAMRI, CEA, France). A sentinel node was defined as any node that was blue, both blue and hot (hot defined as an *in vivo* count of two times the background or more) or hot alone. Pathology No frozen sections were performed. Lymph nodes embedded whole and slices prepared perpendicularly to the nodes largest axis, and 10 4µm sections were prepared. Sections 1, 4 and 7 were stained with H&E and when H&E was negative, IHC was carried out on 3 intermediate sections using an antibody specific for keratin. Micrometastases were defined as metastasis <2mm in size. For nonsentienl nodes, one node per block, one section per block, stained with H&E A standard level I and II lymph node dissection was performed after sentinel lymph node biopsy.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** June 1999 to November 2001 **Operator details** Surgeon A and Surgeon B performed 100 cases each. **Outcome measures** Not applicable	**Sample size** 200 patients **Age** 57, range 30 to 79 years **Type of surgery** The inclusion criteria included patients with indications for conservative surgical treatment, patients indicated for radical surgical treatment were excluded. **Stage of disease**: 2.44, range 1.2 to 6.1cm I: 65/199 (32.7%) II: 89/199 (44.7%) III: 45/199 (22.6%) (Histoprognostic grade not specified in one case) **Tumour histology** Invasive ductal cancer: 149/200 (74.5%) Invasive lobular cancer: 19/200 (9.5%) Carcinoma:other: 32/200 (16.0%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Dale & Williams, 1998 **Institution** Division of Surgical Oncology, Mercer University School of Medicine, Macon, Georgia, USA. **Inclusion/exclusion criteria** Inclusions: all patients, during the time period, were considered for the study. Exclusions: patients with palpable axillary nodes (3), previous excisional biopsy of lymph node (1), inflammatory breast cancer with preoperative radiation and chemotherapy (1), non-consent for sentinel lymph node biopsy (3).	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection After general anaesthesia, 3-5cc of 1% Lymphazurin (isosulfan blue) was injected into the breast tissue in a four-quadrant location surrounding the primary tumour or excisional biopsy site (attempt was made not to inject into the biopsy cavity). Removal of sentinel lymph nodes It was attempted to identify the blue lymphatic channel as it exited the breast parenchyma and entered the primary draining lymph node or sentinel node. A search for a second sentinel node was also carried out prior to axillary clearance. Searches for sentinel nodes were abandoned after 15 minuted when a level I/II and partial level III axillary clearance was performed. Pathology Standard haematoxylin and eosin staining of entire sentinel node specimens were performed.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** July 1, 1995 to December 31 1996 **Operator details** All surgical procedures were performed by the same surgeon (Dale) **Outcome measures** Not applicable	**Sample size** 20 (21 mapping procedures, 1 patient with bilateral breast cancer) **Age** Median 51, range 27 to 80 years **Type of surgery** Breast conserving: 8/21 (38%) Mastectomy: 13/21 (62%) **Stage of disease**: Median tumour size 1.9, range 0.7 to 8.0cm **Tumour histology** Invasive ductal carcinoma: 6/21 (28.6%) Invasive ductal carcinoma with an *in situ* component: 12/21 (57.1%) Lobular carcinoma: 1/21 (4.8%) Inflammatory carcinoma: 2/21 (9.5%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** 2/21 (9.5%) underwent neoadjuvant chemotherapy (histology of tumours were inflammatory carcinoma).

Authors	Intervention	Study Design	Study Population
de Kanter, van Geel, Paul. Van Eijck, Henzen-Logmans, Kruyt, Krenning, Eggermont & Wiggers, 2000. **Institution** Departments of Surgery, Pathology and Radiology, University Hospital Rotterdam/Daniel den Hoed Cancer Center; Department of Surgery, Zuiderziekenhuis Rotterdam; and Departments of Surgery and Nuclear Medicine, University Hospital Rotterdam/Dijkzigt Hospital, The Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients with operable breast cancer, diagnosed by mammography, palpation and cytology, visiting one of three participating hospitals. Exclusions: patients with palpable lymph nodes, necessity for neoadjuvant chemotherapy or multifocal tumours.	Sentinel Lymph Node Biopsy Radioactive colloid and/or dye injection ^{99m}Tc-labelled nanocolloid (Solconanocoll®) was injected subcutaneously and peritumorally, if the tumour had previously been excised, the radiocolloid was injected cranially of the scar in health breast tissue, at least 2.5 hours before operation. A dose of 30 to 40MBq was used, but if surgery was planned for the day after injection, the amount of radiocolloid was doubled. Patent blue dye (0.5ml) was injected intradermally above the tumour, or if the tumour had been previously excised, cranially of the scar, at the beginning of the operation. Removal of sentinel lymph nodes The sentinel nodes were identified with the guidance of a RMD-CTC4 pr C-trac probe and the blue stained lymph vessel. The sentinel node was traced in the axillary specimen in the first 10 patients, later the sentinel node was identified and excised before the axillary clearance. Pathology The sentinel nodes were examined with multiple sections (4 to 8) with H&E and IHC using cytokeratin antibody (CAM 5.2) in order to detect micrometastases.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** December 1996 to November 1998 **Operator details** A total of 12 surgeons performed the procedures in 3 hospitals. **Outcome measures** Not applicable	**Sample size** 232 patients (possibly 1 male patient) **Age** Not stated **Type of surgery** Modified radical mastectomy 40% Modified radical mastectomy after diagnostic lumpectomy 17% Lumpectomy and axillary clearance 29% Axillary clearance alone after diagnostic lumpectomy 14% **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Lateral quadrant, approximately 50%. **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Dupont, Salud, Peltz, Nguyen, Whitehead, Ku, Reintgen & Cox, 2001. **Institution** Comprehensive Breast Program, H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida, Tampa, FL, USA. **Inclusion/exclusion criteria** Inclusions: not stated. Exclusions: not stated Note: also reported in Dupont, Cox, Nguyen, Salud, Peltz, Whitehead, Ebert, Ku & Reintgen, 2001.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Lymphatic mapping was performed using a combination technique. Patients were injected with 450 μCi of filtered (0.2μm filter) Tc 99m labelled sulfur colloid (Syncor International, Tampa, Florida, USA) in 6ml of saline 1 to 6 hr prior to the operation. The injection was administered intraparenchymally in six 1-cc aliquots at the periphery of the lesion or biopsy cavity. Five minutes prior to axillary exploration, approximately 5 ml of isosulfan blue dye (Lymphazurin, US Surgical Corp., Norwalk, Connecticut, USA) was injected intraparenchymally at approximately the same location as the radiocolloid. The breast was compressed and massaged for 5 continuous minutes. For internal mammary mapping, all inner quadrant and central breast lesions were evaluated with preoperative lymphoscintigraphy. Removal of sentinel lymph nodes Meticulous dissection was performed to avoid staining of the surgical field with blood or premature disruption with blue dye. A hand-held gamma probe (GPS/Navigator System, US Surgical Corp., Norwalk, Connecticut) was used to locate the SN and guide intraoperative surgery. The SN was defined as any blue node and any hot node with an *ex vivo* radioactivity count ratio of SN to non-SN of 10:1 or *in vivo* count ration of SN to background of 3:1. Pathology Not stated.	Case series **Level of evidence** Level IV **Follow-up** Not stated. **Loss to follow-up** Not stated. **Study period** April 1998 to November 2000. **Operator details** Not stated. **Outcome measures** Not applicable.	**Sample size** 1470 mapped patients (36/1470 (2.4%) at least one IMN removed) **Age** Mean age 50 yr for 5/36 (14%) with IMN removed and +ve for metastatic disease **Type of surgery** Not stated **Stage of disease** 5 IMN patients had mean tumour size 14 mm T1 4/5 (80%) **Tumour histology** Lobular or mixed ductal and lobular carcinoma 4/5 (80%). **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Chemotherapy and radiation 5/36 (14%)

Authors	Intervention	Study Design	Study Population
Estourgie, Tanis, Nieweg, Valdes Olmos, Rutgers & Kroon, 2003b. **Institution** Departments of Surgery and Nuclear Medicine, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam; Department of Surgery, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands. **Inclusion/exclusion criteria** Inclusions: patients who had internal mammary sentinel nodes identified by preoperative lymphoscintigraphy were offered the option of having the node(s) removed for staging purposes. All patients chose that option. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-labelled nanocolloid (Nanocoll; Amersham Cygne, Eindhoven, The Netherlands) was injected into the lesion on the day before surgery. A mean volume of 0.2ml with a mean radioactivity dose of 3.1mCi (114.9MBq) was injected. If the tumour was nonpalpable, intratumoral injection was guided by ultrasound or stereotaxis. Lymphoscintigraphy was performed at 30 minutes and 4 hours after injection. was used to identify the sentinel node. Removal of (internal mammary) sentinel lymph nodes The next day, 1.0ml of patent blue dye (Blue Patenté V; Laboratoire Guerbet, Aulnay-sous-Bois, France) and a hand-held gamma probe (Neoprobe; Johnson & Johnson Medical, Hamburg, Germany) was used to identify the sentinel node. Exploration of the axilla was always performed, regardless of whether an axillary hotspot was identified, and the parasternal region was explored only in case of lymphoscintigraphic visualisation. Internal mammary chain sentinel nodes were explored either through the incision made for the removal of the primary tumour or through a small separate transverse incision over the intercostal space indicated. The pectoral muscle fibres were split and the intercostal muscles were separated from the rib to expose the fatty tissue along the internal mammary vessels on the surface of the parietal pleura. Ribs were never divided. Pathology Sentinel nodes were formalin fixed, bisected and paraffin embedded and cut at a minimum of six levels at 50- to 150µm intervals. Examination included H&E and IHC with CAM 5.2 *Becton Dickinson, San José, CA, USA).	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** January 1999 to December 2002 **Operator details** All procedures were performed by one of four experienced surgery or under their supervision by a resident or fellow. **Outcome measures** Not applicable	**Sample size** 150 patients (had internal mammary nodes identified) **Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Traditionally, the indication for radiotherapy to the internal mammary chain has been positive axillary lymph node(s). Radiotherapy to the internal mammary chain region was given in 10 patients (10 patients with a tumour-free axillary and a tumour-positive internal mammary chain sentinel node). Radiotherapy was omitted in 11 patients with a tumour free internal mammary chain sentinel node. Adjuvant systemic therapy was given to 14 patients because of a tumour-positive internal mammary chain sentinel node in the absence of axillary metastases or with only micrometastatic involvement of the axilla.

Authors	Intervention	Study Design	Study Population
Feggi, Basaglia, Corcione, Querzoli, Soliani, Ascanelli, Prandini, Bergossi & Carcoforo, 2001. **Institution** Departments of Nuclear Medicine and Radiology, S. Anna Hospital; Departments of General Surgery and Pathology, University of Ferrara, Ferrara, Italy. **Inclusion/exclusion criteria** Inclusions: patients with nonpalpable breast lesions (identified by screening mammography and/or ultrasound), nonpalpable axillary nodes Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Nanocolloidal tracer (Nanocoll, Nycomed Amersham Sorin, Saluggia, Italy; average particle size< 80 nm; labelled with ^{99m}technetium; concentration 5550 Mbq/ml) was injected (average dose 130 MBq (range 110-150); injectate volume 0.3-0.4 cc) in order to have about 10 MBq of radioactivity at time of surgery. Tracer was administered under sonographic or stereotactic guidance. Half the dose (maximum 0.2 ml) was administered intratumourally and half superficially, but very close to the tumour. When the primary lesion had no mass but consisted only of microcalcifications, the entire dose was injected among these calcifications. Using the same needle, a radiographic contrast medium could be injected immediately after tracer injection, in order to confirm positioning of the injectate by mammography. For nonpalpable lesions which appeared only as microcalcifications on mammography, a hook wire was inserted while injecting the tracer under radiological guidance to assist locating the lesion. A breast massage by the patient was encouraged. Removal of sentinel lymph nodes Lymphoscintigraphy was performed. A gamma ray detection probe (Scintiprobe MR 100 or Neoprobe NEO 2000) was used to locate the lesion and to guide its surgical removal. The cutaneous projection of the lesion was located, and a radial cutaneous incision and a wide lesion excision (quadrantectomy) were performed. After specimen excision, the absence of high levels of radioactivity in the residual tissue was verified, and the resected tissue was imaged by scintigraphy and mammography to verify the presence of the lesion in the specimen. Pathology Histological examination after embedding in paraffin was usually requested. Multilevel (100 µm interval) sectioning of the SN was performed, with H&E staining and IHC (anticytokeratin AE1, AE3, PCK26 antibodies).	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not stated **Operator details** The protocol was approved by the hospital Ethics Committee and every patient gave informed consent. **Outcome measures** Not applicable	**Sample size** 73 patients **Age** Median 60, range 46 to 80 years **Type of surgery** Conservative surgery **Stage of disease** Staging (AJCC) 0: 8/73 (11.0%) I: 45/73 (61.6%) IIA: 18/73 (24.7%) IIB: 1/73 (1.4%) IIIB: 1/73 (1.4%) Tis: 9/73 (12.3%) T1a: 6/73 (8.2%) T1b: 15/73 (20.5%) T1c: 41/73 (56.2%) T2: 2/73 (2.7%) N0: 53/73 (72.6%) N1: 19/73 (26.0%) N3: 1/73 (1.4%) M0: 73/73 (100%) **Tumour histology** Infiltrating ductal carcinoma [+ intraductal component]: 34/73 (46.6%) [20] Infiltrating lobular carcinoma [+ intraductal component]: 15/73 (20.5%) [9] Infiltrating lobular + tubular carcinoma: 13/73 (17.8%) Infiltrating cribriform + tubular carcinoma: 2/73 (2.7%) Intraductal carcinoma: 9/73 (12.3%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated

			Adjuvant therapy Not stated

Authors	Intervention	Study Design	Study Population
Galimberti, Veronesi, Arnone, De Cicco, Renne, Intra, Zurrida, Sacchini, Gennari, Vento, Luini & Veronesi, 2002. **Institution** Divisions of Senology, Nuclear Medicine and Pathology, European Institute of Oncology, Milan, Italy; Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA; Divisione di Chirurgia Generale, Fondazione Salvatore Maugeri, Pavia, Italy. **Inclusion/exclusion criteria** Inclusions: patients with breast cancer that showed radioactive uptake to the IMN region, as revealed by lymphoscintigraphy after peritumoral (131 cases) or superficial (16 cases) injection of radiotracer, or tumour location in the medial portion of the breast. 182 consecutive patients underwent IMN exploration with subsequent IMN sampling in 160/182 (88%) patients. Exclusions: 30/182 (16%) patients had no macroscopic lymph nodes identified during surgical exploration of the intercostal space and subsequent pathological testing of the excised adipose tissue revealed no lymph nodes in 22/182 (12%) patients and these patients were not considered further.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Radiotracer was injected before surgery in 147/160 (91.9%) patients. Removal of sentinel lymph nodes Radioactive take-up was observed in IMN area in 95/147 (64.6%) patients. In 52/147 (35.4%) patients whom no take-up was observed in this area and in 13/160 (8.1%) patients in whom no tracer was injected, IMNs were sampled without the aid of a gamma probe. In these 65/160 (40.6%) patients the tumour was always located medial to a vertical line drawn to touch the lateral margin of the areola. Taking into account the anatomy of the lymphatic network of the breast, the second intercostal space was explored if the tumour was located in the inner upper quadrant and the third intercostal space if it was in the lower quadrant. In patients with an IMN identified by lymphoscintigraphy, the node was removed with the aid of a handheld gamma probe. After surgery to remove the breast tumour, breast tissue was detached from the fascia of the pectoralis muscle to provide access to the hot spot or space of interest. If a hot spot had been revealed by lymphoscintigraphy, the probe was used to assist the location and excision of this material. Fatty tissue considered to contain lymph nodes was removed in patients with no tracer take-up in the IMN region or who were not injected with tracer. Pathology All material removed from the subcostal space was sent for permanent section histological analysis, without frozen section examination. In patients undergoing axillary sentinel node biopsy, the sentinel node was examined during surgery to determine whether axillary dissection should be performed immediately.	Case series **Level of evidence** Level IV **Follow-up** Not stated. **Loss to follow-up** Not stated. **Study period** September 1998 to September 2001. **Operator details** Not stated. **Outcome measures** Not applicable.	**Sample size** 160 patients **Age** Mean 52.0 years **Type of surgery** Quadrantectomy: 154/160 (96.3%) Mastectomy: 6/160 (3.8%) **Stage of disease** Mean tumour size, 17.8 mm **Tumour location** Not stated **Tumour location** Left: 72/160 (45%) Right: 88/160 (55%) Central: 6/160 (3.7%) Upper outer: 8/160 (5.0%) Upper inner: 103/160 (64.4%) Lower outer: 4/160 (2.5%) Lower inner: 39/160 (24.4%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** All 14/160 (8.8%) patients with metastatic IMNs received mammary chain radiotherapy.

<table>
<tr><th>Authors</th><th>Intervention</th><th>Study Design</th><th>Study Population</th></tr>
<tr>
<td>Giuliano, Jones, Brennan & Statman, 1997.

Institution
Joyce Eisenberg Keefer Breast Center, John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, CA, USA.

Inclusion/exclusion criteria
Inclusions: none stated
Exclusions: patients with large excisions, prior axillary surgery, clinical T3 lesions or clinically multifocal lesions.</td>
<td>Sentinel Lymph Node Biopsy

Radioactive colloid and/or dye injection
3 to 5 ml isosulfan blue dye (Lymphazurin 1%, Hirsch Industries, Inc, Richmond, VA, USA) was injected into the breast parenchyma immediately surrounding a primary tumour. If tumour had previously been excised, the wall of the biopsy cavity and surrounding tissue were injected. Dye was injected below the subcutaneous fat to avoid skin tattooing and to assure parenchymal uptake by breast lymphatics.

Removal of sentinel lymph nodes
Following dye injection, a separate incision was made in the axilla. The dye-laden lymphatic tract was identified and followed to a blue-stained sentinel node(s), which was excised and processed as a separate specimen. A thorough search for any additional blue nodes was performed before standard ALND through the same incision. Axillary clearance removed level I, II and a small portion of III axillary nodes. If axilla was grossly involved, all level III nodes were removed.

Pathology
SNs were bivalved and a frozen section was obtained to confirm presence of nodal tissue. Frozen tissue was then processed routinely for permanent section with H&E. Each node was blocked individually, resulting in two permanent section levels per paraffin block. A cytokeratin IHC (MAK-6; Ciba-Corning, Alameda, CA, USA) was performed on all SNs that showed no metastases with H&E. Approximately six to eight histologic faces were examined per SN. Non-sentinel nodes (ALND) were processed routinely and one or two levels of each node were examined with H&E. IHC was not undertaken unless routine H&E detected suspicious but not diagnostically malignant cells.</td>
<td>Case series

Level of evidence
Level IV

Follow-up
Not stated

Loss to follow-up
Not stated

Study period
July 1994 to October 1995

Operator details
All operations were performed by the same surgeon (AEG) after informed consent. All axillary specimens were examined by pathologists at Saint John's Health Center. The SLND specimen was evaluated independently of the ALND specimen.

Outcome measures
Not applicable</td>
<td>Sample size
107 patients

Age
Median 56.6, range 28 to 90 years

Type of surgery
Conservative surgery 93/107 (86.9%)
Mastectomy 14/107 (13.1%)

Stage of disease
Mean tumour size 21.1±13.8, range 1 to 75mm
One SN was identified in 100 patients with following tumour sizes:
<table>
<tr><td>T1a</td><td>4/100 (4%)</td></tr>
<tr><td>T1b</td><td>18/100 (18%)</td></tr>
<tr><td>T1c</td><td>42/100 (42%)</td></tr>
<tr><td>T2</td><td>34/100 (34%)</td></tr>
<tr><td>T3</td><td>2/100 (2%)</td></tr>
</table>
Tumour histology
<table>
<tr><td>Invasive ductal carcinoma</td><td>98/107 (91.6%)</td></tr>
<tr><td>Invasive lobular carcinoma</td><td>9/107 (8.4%)</td></tr>
</table>
Tumour location
Not stated

Receptor status
<table>
<tr><td>Oestrogen receptor positive</td><td>85/107 (79.4%)</td></tr>
<tr><td>Progesterone receptor positive</td><td>69/107 (64.5%)</td></tr>
</table>
Menopausal status
<table>
<tr><td>Premenopausal</td><td>44/107 (41.1%)</td></tr>
<tr><td>Postmenopausal</td><td>63/107 (58.9%)</td></tr>
</table>
Adjuvant therapy
Not stated</td>
</tr>
</table>

Authors	Intervention	Study Design	Study Population
Guenther, Krishnamoorthy & Tan, 1997. **Institution** Department of Surgery, Kaiser Permanente Medical Center, Los Angeles, California, USA. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Injection of approximately 3 to 5 cc of isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Inc, Richmond, VA) with a 25-gauge needle near the primary tumour site in a circumferential pattern. If the gross tumour was present, dye was injected at the tumour-breast interface. Patients treated after excisional biopsy underwent injection of blue dye into the biopsy cavity walls. Three to 5 minutes of breast massage was performed to stimulate lymphatic flow. Removal of sentinel lymph nodes For patients undergoing segmental mastectomy and node dissection, a transverse skin incision was made beneath the hair-bearing area of the axilla. For patients choosing mastectomy, lateral portion of the upper skin incision was opened prior to flap elevation. The superficial axillary tissue and clavipectoral fascia were gently dissected until a blue lymphatic channel or node(s) was identified. Blue channel(s) were traced into the breast to ensure the SN was correctly identified. The SN was excised and sent as a separate specimen. If a sentinel node was not identified within 10 minutes, further exploration was omitted. A standard level I and II ALND was completed for patients with invasive breast cancer. Pathology Pathological analysis of the SN consisted of serial sectioning of the node into about five segments, which were stained with H&E. IHC was not routinely employed. The non-SN axillary lymph nodes were routinely sectioned, stained with H&E and analysed.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** September 1994 to June 1996. **Operator details** All operations were performed by one of two attending surgeons (LRT and JMG) assisted by surgical residents. The senior surgeon (JMG) had observed 15 intraoperative lymphatic mapping and sentinel lymphadenectomy previously and the other surgeon (LRT) had no previous experience. All patients were treated at the Kaiser Permanente Medical Center. Informed consent was obtained in all cases. **Outcome measures** Not applicable	**Sample size** 145 **Age** Mean 55.3, range 33 to 88 years **Type of surgery** Conservative surgery: 95/145 (65.5%) Mastectomy: 50/145 (34.5%) **Stage of disease** Mean tumour size, 20.9, range 6 to 70 mm Grade 1: 29/145 (20%) Grade 2: 58/145 (40%) Grade 3: 38/145 (26%) Not reported: 20/145 (13.8%) T1: 66/145 (45.5%) T2: 46/145 (31.7%) T3: 3/145 (2.1%) T4: 1/145 (0.7%) Tis: 6/145 (4.1%) Not reported: 23/145 (15.9%) **Tumour histology** Ductal: 130/145 (89.7%) Lobular: 8/145 (5.5%) DCIS: 7/145 (4.8%) **Tumour location** Not stated **Receptor status** Oestrogen receptor positive: 96/138 (69.6%) Progesterone receptor positive: 78/105 (74.3%) **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Hansen, Grube & Giuliano, 2002. **Institution** Joyce Eisenberg Keefer Breast Centre, John Wayne Cancer Institute, St John's Health Center, Santa Monica, CA, USA. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: patients with rimary tumours >5cm, multicentric tumours, locally advanced disease, ductal carcinoma *in situ*, stage IV disease at presentation or patients enrolled in ACOSOG trials.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Intraoperative lymphatic mapping performed using 1% vital blue dye solution (Lymphazurin; US Surgical, Norwalk, CT, USA). 3-5ml of dye was injected into the parenchyma surrounding the tumour or into the wall of the biopsy cavity. Dye was injected around the localizing wires in the case of non-palpable tumours. Technetium 99m filtered sulphur colloid was also used as a mapping agent in selected cases. Removal of sentinel lymph nodes The breast was manually compressed for 3 to 7 mins after the injection of dye and an incision approximately 1cm below the hairline was made in the axilla. All blue stained lymphatics were identified and traced proximally and distally to each blue-stained sentinel node. After all sentinel or suspicious nodes were identified and excision, a breast conserving procedure was performed Pathology Sentinel nodes were examined at 2 step-section levels of each paraffin block, each separated by 40 micrometers and H&E stained at each level. IHC (monoclonal anticytokeratin antibody cocktail, Zymed Laboratories, San Francisco, CA, USA) was performed if no metastases were identified with H&E. (Early in the study, sentinel nodes were examined intraoperatively by frozen section, but this was abandoned.)	Case series **Level of evidence** Level IV **Follow-up** Median 38.9, range 6 to 69 months **Loss to follow-up** Not stated **Study period** October 1 1995 to April 30 1999 (in May 1999 authors began enrolling patients into the ACOSOG trials – none of these patients are included in this study). **Operator details** Not stated **Outcome measures** Patients were followed-up and examined at 1 and 4 weeks postoperatively and then every 6 months for 2 years thereafter. Mammography was performed biannually for the first 2 years and then annually.	**Sample size** 238 patients **Age** Median 58.4, range 29 to 89 years **Type of surgery** Breast conserving surgery **Stage of disease** Median tumour size 1.3cm, range 1mm to 4.5cm Stage I: 85% Stage IIa: 15% **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Oestrogen receptor positive: 184/238 (77.3%) Progesterone receptor positive: 146/238 (61.3%) **Menopausal status** Premenopausal: 21% Peri- or postmenopausal: 79% Note: perimenopausal defined as having a menstrual cycle within the past year. **Adjuvant therapy** Decisions were made by a team consisting of the surgeon and the medical and radiation oncologists. External beam radiation: 219/238 (92%) Chemotherapy alone: 11% Tamoxifen alone: 42% Chemotherapy and Tamoxifen: 13.6% External beam radiation (40-50Gy) to the whole breast as tangential fields with a boost of 60Gy to the tumour bed [All patients advised, 19 refused]

Authors	Intervention	Study Design	Study Population
Ilum, Bak, Olsen, Kryh, Berg & Axelsson, 2000. **Institution** Departments of Surgery and Pathology, Odense University Hospital, Odense, Denmark. **Inclusion/exclusion criteria** Inclusions: patients with operable primary breast cancer (including patients with enlarges axillary nodes, patients with multifocal or bilateral tumours and patients with a previous excisional biopsy) and informed consent. Exclusions: patients who had previous axillary dissection or neoadjuvant chemotherapy.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection In theatre, immediately after induction of general anaesthesia, 0.5 ml patent blue V (2.5%, Laboratoire Guerbet, France) was injected intradermally over the primary tumour. In the case of tumour excision having already been performed, 1.0 ml was injected intradermally 2 cm in axillary direction from the cicatrix. After the first 103 SN dissections, an additional 0.25 ml patent blue V was injected subdermally. No massage of the injection site was performed. Removal of sentinel lymph nodes The SN was defined as either a blue lymph node or a lymph node with blue lymphatics entering the capsule. In modified radical mastectomy, dissection was done through upper lateral part of usual incision. Blue lymphatic vessels were followed by careful dissection until a blue node was encountered and excised. If blue nodes were found intimately coherent with other nodes, the packet was excised in toto. Mastectomy and axillary lymphadenectomy were then completed. In conservative surgery, SN was located through a transverse incision distal to the axilla, followed by axillary lymphadenectomy. First 103 operations SN excision and lymphadenectomy were performed after lumpectomy, and this was reversed in the remaining 58 operations. Localisation of SN was allowed no more than 15 min operating time. Pathology All specimens were dissected fresh without node-clearing techniques. If SN specimen contained more than one node, all were considered SNs. A blue node in the axillary specimens were considered a SN. Nodes >4 mm were bisected and all nodes were embedded separately. No frozen sections were taken. For non-sentinel nodes, permanent sections were cut from two levels and stained with H&E, and for SN, permanent sections were cut from one level and stained with H&E. If no metastasis was found, step-sectioning was done at six levels and slides stained with IHC using CAM 5.2 (Becton-Dickinson). Immunostain was considered positive, if malignant-looking immunoreactive cells were identified within the node (individually or clustered).	Case series. **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** August 1998 to June 1999 **Operator details** Ten surgeons, all experienced in axillary dissections, participated. One surgeon (CKA) performed 104 operations (mastectomy 38, lumpectomy 66) and the remaining nine surgeons performed from one to 15 operations (median 5). The principal investigator (CKA) had conducted a small pilot study of SN dissection (not included in this study) and the other surgeons were initially supervised in their first three to six operations (included). **Outcome measures** Not applicable	**Sample size** 159 patients (161 cases, 2 bilateral) **Age** Mean 59, range 28 to 84 years **Type of surgery** Modified radical mastectomy 67/161 (41.6%) Lumpectomy plus axillary lymphadenectomy 94/161 (58.4%) **Stage of disease** Mean tumour size for ductal carcinoma (diameter), 17, range 2 to 55mm **Tumour histology** Invasive ductal carcinoma: 126/161 (78.3%) Invasive lobular carcinoma: 19/161 (11.8%) Invasive ductal carcinoma of special type: 16/161 (9.9%) **Tumour location** Medial: 46/161 (28.6%) Lateral: 107/161 (66.5%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Imoto & Hasebe, 1999. **Institution** Division of Breast Surgery, National Cancer Center Hospital East, Kashiwa, Chiba; Pathology Division, National Cancer Center Research Institute East, Kashiwa, Chiba, Japan. **Inclusion/exclusion criteria** Inclusions: patients with stage 0-IIIB breast cancer according ti the UICC criteria. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Under general anesthesia, 4-5 ml of indigocarmine (4mg/ml) (Daiichi Pharmaceutical, Tokyo, Japan) was injected subcutaneously at two or three sites around the primary tumour. The breast lesions were rubbed well. If the primary tumour had already been excised, the dye was injected near the scar. Removal of sentinel lymph nodes In patients undergoing total mastectomy, first the whole breast was removed from the pectoralis major muscle. When the axillary the fat pad was exposed, the SNs were identified after lymphatic mapping. Usually blue-stained lymph nodes or dye-filled lymphatic tracts were easily identified in a few minutes. Whenever blue-staining afferent lymphatic tracts were traced to lymph nodes partly stained blue, they were excised as SNs. In patients undergoing conservative surgery, partial mastectomy was performed 15 min after subcutaneous injection of indigocarmine and then SNB was performed. Pathology Pathological diagnosis was based on examination of paraffin-embedded H&E stained sections of the primary tumour and all axillary lymph nodes. In some cases, SNs were immediately diagnosed histologically by frozen-section examination. ALND was completed up to levels I and II or more. If the primary tumour was located in the inner or lower region of the breast, ALND was performed through a separate skin incision following SNB.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** January to July 1998 **Operator details** Informed consent with SNB obtained before the surgical procedure. **Outcome measures** Not applicable	**Sample size** 86 patients (88 mapping procedures, 2 patients with bilateral breast cancer) **Age** Median 53, range 30 to 81 years **Type of surgery** Mastectomy: 55/88 (62.5%) Conservative surgery: 33/88 (37.5%) **Stage of disease** Tumour size, median 3.0, range 0.0 to 12.0cm 0 or I: 26/88 (29.5%) IIA: 34/88 (38.6%) IIB: 13/88 (14.8%) IIIA: 11/88 (12.5%) IIIB: 4/88 (4.5%) N0: 61/88 (69.3%) N1: 23/88 (26.1%) N2: 4/88 (4.5%) **Tumour histology** Non-invasive ductal carcinoma: 4/88 (4.5%) Invasive ductal carcinoma with predominant intraductal component: 8/88 (9.1%) Invasive ductal carcinoma: 64/88 (72.7%) Invasive lobular carcinoma: 6/88 (6.8%) Other: 6/88 (6.8%) **Tumour location** UOQ: 43/88 (48.9%) UIQ: 28/88 (31.8%) LOQ: 3/88 (3.4%) LIQ: 2/88 (2.3%) Central: 8/88 (9.1%) Whole: 4/88 (4.5%) **Receptor status** ER positive: 27/88 (30.7%) ER negative: 51/88 (58.0%) ER status unknown: 10/88 (11.4%) PR positive: 33/88 (37.5%) PR negative: 45/88 (51.1%) PR status unknown: 10/88 (11.4%)

			Menopausal status Premenopausal: 40/86 (46.5%) Post menopausal: 46/86 (53.5%) **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Jansen, Doting, Rutgers, de Vries, Valdés Olmos & Nieweg, 2000. **Institution** Departments of Surgery* and Nuclear Medicine, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam and Department of Surgical Oncology, Groningen, the Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients with an operable palpable breast tumour that appeared malignant on clinical examination, imaging (mammography, ultrasonography or both) and fine-needle aspiration cytology. Exclusions: patients with previous excision biopsy, clinical evidence of axillary lymph node metastasis or pregnancy. Note: also Rutgers & Nieweg, 2000.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Patients were injected intratumorally with 0.2ml 40-60MBq Tc 99m (Nanocoll, Sorin Biomedica Diagnostics, Saluggia, Italy) one day befefore surgery. Immediately before surgery, 1.0ml patent blue dye (Bleu Patenté V; Laboratoire Guerbert, Aulnay-sous-Bois, France) was injected into the tumour. Lymphoscintography was performed one day before surgery. Removal of sentinel lymph nodes A hot spot was considered to represent a sentinel node if an afferent lymphatic vessel coming from the injection site was visualised. If no afferent vessels visualised, the surgeon was advised to search the axilla and internal mammary chain for the first nodes that appeared on the lumphoscintigraphy images. Sentinel biopsy was performed as described elsewhere (Rutgers *et al.* 1998). Sentinel nodes were sought in the axilla through an incision at the border of the pectoralis major muscle by following blue-stained lymphatic vessels or by the gamma probe (Neoprobe 1000/1500), Neoprobe, Dublin, Ohio, USA). Level I-II of the axilla were explored when lymphoscintigraphy revealed hot spots there. All SNs that would be not be removed in a routine Level I-II axillary clearance are referred as SNs outside the axilla. Sentinel node biopsy was followed by level I-II (or III) axillary clearance regardless of node status. Pathology Sentinel (and non-sentinel nodes) were embedded and stained with H&E and examined with IHC for cytokeratin (CAM 5.2) at a minimum of at least three levels. Nodes <1 cm were embedded in two halves in one block and larger nodes in parallel slices of 0.2cm in more than one block. All blocks were cut at three levels at 100µm intervals. Additional nodes from axillary dissection were evaluated at one or two levels including IHC.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** October 1996 to June 1998 **Operator details** Performed at two tertiary care hospitals following same protocol. **Outcome measures** Not applicable	**Sample size** 113 patients **Age** Mean 58, range 33 to 89 years **Type of surgery** Mastectomy 50% Conservative surgery 50% **Stage of disease** T1 55/113 (49%) T2 52/113 (46%) T3 6/113 (5%) **Tumour histology** Not stated **Tumour location** UOQ 48/113 (42%) UIQ 22/113 (19%) LOQ 20/113 (18%) LIQ 10/113 (9%) Central 13/113 (12%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** 3/113 (2.7%) tumour-positive SNs in the internal mammary chain and received radiotherapy to internal mammary chain. One patient of these three (1/113 (0.8%)) had no metastases in the axilla and also received adjuvant systematic treatment that would otherwise not have been given.

Authors	Intervention	Study Design	Study Population
Johnson, Soot, Nelson, Franzini, Vea, Gruner, Kulawiak & Young, 2000. **Institution** Legacy Cancer Services, Good Samaritan Hospital, Department of Surgery, Oregon Health Sciences University, Portland, Oregon, USA. **Inclusion/exclusion criteria** Inclusions: patients diagnosed with breast cancer via FNA, stereotactic or excisional biopsy. Exclusions: patients with clinically positive nodes.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection After informed consent, patients were admitted at least 2 hr prior to scheduled surgery and underwent injection of I millicurie or Tc 99m. The tracer was injected with ultrasound guidance into four points around the tumour or biopsy cavity and volume ranged from 4 cc to 8 cc. Removal of sentinel lymph nodes Nuclear medicine imaging was performed in all cases. Intraoperatively the surgeons identified the zone of injection activity and scanned the regions around the breast to identify hot spots in the internal mammary, supraclavicular and axillary basins using a gamma probe (C-Trak, Carewise Medical Products, Morgan Hill, CA, USA). All hot spots were marked and SNs excised using the gamma probe for delineation of hot nodes. Internal mammary SNs (IMSN) found on nuclear imaging were identified in the operating room and subsequently excised. In patients undergoing lumpectomy, a separate transverse incision was made over the delineated hot spot in the appropriate intercostal space. All patients had excision of axillary SNs and a complete axillary node dissection. Pathology Not stated.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 80 patients **Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Central/inner 32/80 (40%) (4/32 (12.5%) IM node drainage) Outer 48/80 (60%) (6/48 (12.5%) have IMSN) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Kapteijn, Nieweg, Peterson, Rutgers, Hart, van Dongen & Kroon, 1998. **Institution** Departments of Surgery, Pathology and Radiotherapy, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, the Netherlands. **Inclusion/exclusion criteria** Inclusions: patients scheduled for a modified radical mastectomy or segmental mastectomy with *en bloc* lymph node dissection that had clinical palpable breast cancer confirmed by mammography and FNA-cytology, absence of multicentric breast cancer and absence of clinically suspected nodal and/or distant metastases. Patients should not have undergone prior treatment, except for a level III axillary biopsy. Exclusions: pregnant patients.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Under general anaesthesia and after preparing and draping the surgical field, 1 ml patent blue dye was injected into the tumour with a 21-gauge needle. To ensure an even distribution, dye was administered in three injections from different angles. Removal of sentinel lymph nodes Immediately after blue dye injection, a standard mastectomy or segmental mastectomy with *en bloc* AC was performed, including level I and II nodes and sometimes level III nodes. During surgery, special note was made of the drainage pattern of blue-coloured lymphatic vessels. The site of injection was excised with surrounding skin. Pathology Specimen was dissected in the pathology department and blue-stained vessels were traced and dissected to a SN. SNs were excised and submitted separately for H&E and CAM 5.2 (Becton Dickinson, San José, CA, USA) IHC staining. Remaining nodes were counted and evaluated in similar fashion.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** June 1994 to June 1996. **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 30 patients **Age** Mean 57, range 35 to 82 years **Type of surgery** Mastectomy or segmental mastectomy with *en bloc* ALND. **Stage of disease** Mean tumour size (diameter), 29, range 11 to 50mm **Tumour histology** Invasive ductal carcinoma: 22/30 (73.3%) Lobular invasive carcinoma: 5/30 (16.7%) Ductolobular invasive carcinoma: 2/30 (6.7%) Ductal carcinoma *in situ*: 1/30 (3.3%) **Tumour location** UOQ: 21/30 (70%) UIQ: 3/30 (10%) LOQ: 1/30 (3%) LIQ: 2/30 (7%) Central: 3/30 (10%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Koller, Barsuk, Zippel, Engelberg, Ben-Ari & Papa, 1998. **Institution** Breast Cancer Service and Department of Surgical Oncology, Chaim Sheba Medical Center, Tel Hashomer and Tel Aviv University Medical School, Ramat Aviv, Israel. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 3-5 cc of coloured dye (methylene blue 1% or patent blue V dye) was injected subcutaneously at the biopsy site around the region of the tumour, at the time of excision or relumpectomy. Removal of sentinel lymph nodes Ten minutes after injection, an axillary incision was made and the axillary contents were exposed. The lymphatic ducts which were stained with dye material, were followed until the sentinel node or group of nodes were identified. These nodes were excised and sent separately for pathological examination. Subsequent axillary dissection was performed in the usual manner. Pathology Not stated	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 98 patients **Age** Mean 55±14, range 37 to 70 years **Type of surgery** Not stated **Stage of disease** Mean tumour size, 23±8.6 mm Grade I: 15/98 (15.3%) Grade II: 49/98 (50.0%) Grade III: 34/98 (34.7%) **Tumour histology** Infiltrating ductal carcinoma: 90/98 (91.8%) Infiltrating lobular carcinoma: 8/98 (8.2%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Luini, Gatti, Frasson, Naninato, Magalotti, Arnone, Viale, Pruneri, Galimberti, De Cicco & Veronisi, 2002. **Institution** Divisions of Senology, Pathology and Nuclear Medicine, European Institute of Oncology, Milan, Italy; The Pontifica Universita Cattolica, Rio Grande del Sud, Brazil. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Patients were injected with colloidal human albumin particles labelled with Tc99m on the day of or the day prior to surgery. Removal of sentinel lymph nodes Using intradermic local anaesthetic (with IV pain relief and anti anxiety medication if need be), cutaneous and subcutaneous incisions, 3 to 4cm long were made and the axillary fascia was opened exposing the axillary cavity. The gamma probe (Neoprobe; Ethicon Endosurgery, Cincinnati, Ohio) was moved inside the surgical breech until the SN was clearly localized, then the adipose tissue was dissected until the SN was completely isolated and the radioactivity was measured to confirm its identification. The procedure was concluded by the coagulation of blood in the SN and the section of the lymphatic vessels. After excision, the surgeon checked the radioactivity of the excised node and of the surgical breech to look for additional radioactive nodes. Pathology SNs were fixed uncut, if less than 5mm or if 5 to 10mm thick, nodes were bisected along the major axis. If thicker than 1cm, nodes were sliced at 3 to 4mm intervals before being fixed. After fixing, tissue was paraffin embedded and pairs of sections were cut at 50μm intervals until completely sectioned. One section of the pair was stained with H&E and the other was kept for immunohistochemical localization of cytokeratin, using the MNF116 monoclonal antibody (Dako, Glostrup, Denmark), if there were atypical cells suspicious for malignancy by H&E. Metastatic foci <2mm were reported as micrometastases.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** September 2000 to December 2001 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 115 patients **Age** Mean 54 , range 27 to 77 years **Type of surgery** Conservative surgery 1 week after SLNB **Stage of disease** Invasive T1/T2-N0, tumours <2.5mm **Tumour histology** Ductal infiltrating carcinoma 79/115 (68.7%) Lobular infiltrating carcinoma 13/115 (11.3%) Other 21/115 (18.3%) Non-infiltrating carcinoma 2/115 (1.7%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Meijer, Torrenga & Van der Sijp, 2002. **Institution** VU Medisch Centrum, afd. Chirurgische Oncologie, Amsterdam, The Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Lymphoscintigraphy was performed two hours after peritumoral injection of 99mTc nanocolloid. Immediately prior to the procedure approximately 0.5ml patent blue V (Bleu patent'e V "Guerbet") was injected peritumoral or periareolar. Removal of sentinel lymph nodes The sentinel node was localised in the axilla, by gamma probe and visualisation of blue nodes, and removed. If the pathologist found tumour tissue in the lymph node via frozen section, axillary dissection was performed during the same operative procedure. Pathology Intraoperative frozen section. Sentinel nodes were examined postoperatively with haematoxylin and eosin and cytokeratin antibody (monoclonal antibody CAM 5.2) on five levels with an interval of 250µm.	Case series **Level of evidence**Level IV **Follow-up** Minimum 36 months Median 47 months (Patients seen every three months during first year, every 6 months after one year, and an annual mammogram was performed). **Loss to follow-up** Not stated **Study period** Not stated **Operator details** Not stated **Outcome measures** Clinical examination and mammography.	**Sample size** 100 patients **Age** Average 55, range 33 to 81 years **Type of surgery** Breast conserving surgery **Stage of disease** T1 or T2, average diameter 1.5, range 0.4 to 5.0cm **Tumour histology** Ductal carcinoma: 91 (91.0%) Lobular carcinoma: 9 (9.0%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Hormonal: 5/100 (5.0%) Standard chemotherapy: 8/100 (8.0%) Combination: 7/100 (7.0%) Note: applied in accordance following International guidelines under the basis of the variables – primary size of tumour, hormone receptor status, mitotic index and age. Local radiotherapy all patient who received breast conserving surgery.

Authors	Intervention	Study Design	Study Population
Miner, Shriver, Jaques, Maniscalco-Theberge & Krag, 1999. **Institution** General Surgery Service, Walter Reed Army Medical Center, Washington DC; The Vermont Cancer Center, Burlington, Vermont, USA. **Inclusion/exclusion criteria** Inclusions: nonpregnant patients with biopsy-proven breast cancer. No patient was excluded on the basis of biopsy type or whether the patient had a palpable lesion at the time of the procedure. Exclusions: patients with multicentric breast cancer or noninvansive breast cancer. Note: also reported in Miner, Shriver, Jaques, Maniscalco-Theberge & Krag, 1998.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-labelled unfiltered sulphur colloid (1mCi in 4.0ml saline) was injected around the perimeter of the breast lesion, nonpalpable masses or prior biopsy sites were injected utilizing US guidance. It was not stated whether preoperative lymphoscintigraphy was performed. Blue dye was not used. Removal of sentinel lymph nodes Radiolocalisation was performed with a hand-held gamma probe (C-Trak®; Care Wise Medical Products, Morgan Hill, CA, USA), and hotspots were identified (areas having greater than 25 counts per 10 seconds and a target to background ratio of greater than 3:1) and all radioactive lymph nodes under a hotspot were excised. Pathology All removed nodes were fixed in formalin and routinely processed and evaluated with H&E stained sections. 57/82 (69.5%) received a complete axillary lymph node dissection. Subsequent patients were offered sentinel node biopsy with or without full axillary lymph node dissection. They were not offered sentinel node biopsy alone if they had lesions greater than 3cm or palpable axillary nodes. Patients who were found to have metastatic disease in the sentinel node had a completion axillary dissection at a later date.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** April 1996 to December 1998 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 82 patients (81 female:1 male) **Age** Mean 55.2 ± (SD) 1.5, median 58.7 years **Type of surgery** Partial mastectomy: 43/82 (52.4%) Total mastectomy: 26/82 (31.7%) Axillary clearance and/or sentinel node biopsy only: 13/82 (15.9%) **Stage of disease** Mean 1.8 ±(SD) 0.16cm **Tumour histology** Infiltrating ductal carcinoma: 90% Infiltrating lobular carcinoma: 10% **Tumour location** Lateral: 58% Medial: 30% Central: 12% **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Moffat, Gulec, Sittler, Serafini, Sfakianakis, Boggs, Franceschi, Pruett, Pop, Gurkok, Livingstone & Krag, 1999. **Institution** Division of Surgical Oncology, Division of Nuclear Medicine and Department of Pathology, University of Miami Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital, Miami, Florida; the Division of Surgical Oncology, Vermont Cancer Center; and University of Vermont College of Medicine, Burlington, Vermont, USA. **Inclusion/exclusion criteria** Inclusions: patients aged 18 years or older with a Karnofsky performance status of at least 70, who were scheduled to undergo total or segmental mastectomy with axillary lymphadenectomy for unifocal, invasive, cN- breast cancer. Exclusions: patients with m edical factors adversely affecting risk for general anaesthesia. Note: also reported in Gulec, Moffat, Carroll, Serafini, Sfakianakis, Allen, Boggs, Escobedo, Pruett, Gupta, Livingstone & Krag, 1998.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Unfiltered Tc 99m sulfur colloid (^{99m}TcSC, Mallinckrodt, St Louis, MO) 1 mCi in normal saline was injected into the normal breast parenchyma in four equal aliquots around the primary tumour or biopsy cavity. The volume totalled 4 ml in 61 patients and 8 ml in 9 patients. When no hot spots were identified on initial mapping, four aliquots of 10 ml normal saline were injected superior, inferior, medial and lateral to the primary tumour site and mapping was repeated after 10 minutes. Removal of sentinel lymph nodes Patients were taken to the operating room within 8 hr of radiocolloid injection. SLNB was performed under the same general anaesthetic as the definitive cancer operation, including axillary lymphadenectomy. The C-Trak GDP (CareWise Medical, Morgan Hill, CA) was used to map radioactivity. Cutaneous hot spots (discrete foci of radioactivity within a 10-second count of at least 25) were marked and counted. SLNB was directed by the probe. All specimen with at least 10% ex vivo count of the hottest specimen were considered sentinel, and SLNB was deemed complete when a 10 sec count ot the SN bed was less than 10% of the hottest SN. Total axillary lymphadenectomy was then performed. In patients with internal mammary hot spots, SLNB was performed as previously described (Gulec *et al.* 1998). Pathology All lymph nodes were bivalved, and two sections from each were examined by light microscopy after H&E.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Not clear, but SLNB was performed in University of Miami Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital since November 1995. **Operator details** Previous written consent was obtained from all patients. **Outcome measures** Not applicable	**Sample size** 70 patients **Age** Mean 54±10, range 34 to 86 years **Type of surgery** Not stated **Stage of disease** Mean tumour size, 18 ± 12 , median 5, range 1 to 60mm T1: 45/70 (64.3%) T2: 23/70 (32.9%) T3: 2/70 (2.9%) **Tumour histology** Infiltrating ductal not otherwise stated: 57/70 (81.4%) Colloid/mucinous: 3/70 (4.3%) Tubular: 1/70 (1.4%) Papillary: 1/70 (1.4%) Infiltrating ductal and lobular: 3/70 (4.3%) Infiltrating lobular: 5/70 (7.1%) **Tumour location** UOQ: 17/70 (24.3%) UIQ: 11/70 (15.7%) LOQ: 2/70 (2.9%) LIQ: 3/70 (4.3%) Central: 13/70 (18.6%) Superior: 10/70 (14.3%) Lateral: 9/70 (12.9%) Inferior: 3/70 (4.3%) Medial: 2/70 (2.9%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Mokbel & Mostafa, 2001. **Institution** St George's Breast Cancer Centre, St George's Hospital, London, UK. **Inclusion/exclusion criteria** Inclusions: patients with operable infiltrating carcinoma and clinically negative axilla. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 1 ml of methylene blue (1%) was injected subdermally (23 gauge needle) in the subareolar region after the patient had been anaesthetised. Injection site was subsequently massaged for approximately 1-2 minutes. Removal of sentinel lymph nodes Within 5 to 10 min of dye injection, an incision was made in the axilla (transverse or vertical) and blue lymphatics or blue nodes were searched. SN was defined as a blue node or a node receiving a blue lymphatic. Axillary clearance was performed in all cases. Pathology Not stated.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Patients recruited at institution over four-month period. **Operator details** Not stated **Outcome measures** Not stated	**Sample size** 35 patients **Age** Mean 58, range 31 to 85 years **Type of surgery** Conservative surgery: 18/35 (51.4%) Mastectomy: 17/35 (48.6%) **Stage of disease** Mean tumour size, 18.9, range 7 to 40mm T2 (>20 mm): 16/35 (45.7%) Grade I: 6/35 (17.1%) Grade II: 12/35 (34.3%) Grade III: 17/35 (48.6%) **Tumour histology** Not stated **Tumour location** UOQ: 22/35 (63%) UIQ: 2/35 (6%) LOQ: 7/35 (20%) Central: 4/35 (11%) Multifocal: 3/35 (9%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Montgomery, Thorne, Van Zee, Fey, Heerdt, Gemignani, Port, Petrek , Cody & Borgen, 2002. **Institution** Breast Service, Department of Surgery and Department of Anesthesia, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: 22 patients were not given ISB (15 due to previous sulfa allergy history).	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection As part of the mapping procedure (previously described in Cody et al., 2001) ISB (Lymphazurin 1%; Ben Venue Laboratories Inc., Bedford, OH, USA) is injected intraparenchymally into the breast tissue adjacent to the tumour or biopsy cavity. Injected in the operating theatre just before the surgical procedure. Removal of sentinel lymph nodes Not stated Pathology Not stated	Case series (retrospective chart review) **Level of evidence** Level IV **Follow-up** Not stated and not applicable **Loss to follow-up** Not stated and not applicable **Study period** September 12, 1996 to August 17, 2000 (Memorial Sloan-Kettering Cancer Center adverse drug reaction reports and quality-assurance incident reports involving isosulfan blue dye during this period was also reviewed). **Operator details** Not stated **Outcome measures** Not stated	**Sample size** 2392 patients (2464 cases, 50 bilateral for the purposes of this study, the patients were only counted once as ISB exposure occurred only once during the surgery.) **Age** Not stated **Type of surgery** Breast conservation (lumpectomy or reexcision) and SLNB under monitored sedation with local anaesthetic. Mastectomy (and/or) AC with general anaesthesia. **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Mostafa & Carpenter, 2001. **Institution** St Bartholomew's Hospital, Breast Unit, West Smithfield, London, UK. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 1ml of 1% methylene blue dye was subdermally injected in the subareolar region. A single injection of Tc99m non-colloid injected subcutaneously at the areolar margin preoperatively to aid identification. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** April 200 to April 2001 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 80 cases **Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Paganelli, Galimberti, Viale, Veronesi, Intra, De Cicco & Veronesi, 2002. **Institution** Divisions of Nuclear Medicine, Senology and Pathology, European Institute of Oncology, Milan, Italy. **Inclusion/exclusion criteria** Inclusions: patients with palpable mammary lesions of the inner quadrants suspected to be malignant after clinical examination, mammography and fine-needle aspiration. Exclusions: pregnant or lactating women, subjects previously submitted to biopsy and/or radiotherapy of the breast, subjects previously receiving chemotherapy and patients with outer-quadrant lesions because an additional excision would have been required.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The day before surgery, an injection of 10 to 15 MBq (mean 12 MBq) of Tc 99m in 0.1 to 0.2 ml was administered deeply in the breast, under the lesion and just above the pectoral muscle, followed by 0.1 ml of air. Lymphoscintigraphy was performed 15 to 30 min and 3 hr after tracer injection. An additional scan was performed 16 to 18 hr after injection in patients who did not show any tracer migration to internal mammary chain (IMC) and axillary nodes. Removal of sentinel lymph nodes The skin projections of the SNs (axillary and IMC) were marked with a pen. After surgery to remove the breast tumour, breast tissue was detached from the fascia of the pectoralis major to provide access. The longitudinal fibres of the pectoralis muscle were divided to expose the sternum and two ribs and their intercostal muscle immediately above the hot spot or space of interest. A short strip of intercostal muscle adjacent to sternum was removed to provide access to subcostal space and expose the internal mammary vein and artery, which were surrounded by fatty tissue containing small lymph nodes. The fatty tissue was carefully removed from the blood vessels. A gamma-detecting probe was used to help in with the location and excision of the node(s). Pathology All material removed from subcostal space was sent for permanent section histologic analysis without frozen section examination. For patients undergoing axillary sentinel node biopsy, the sentinel node was examined intraoperatively to determine whether axillary dissection should be performed.	Case series (pilot study) **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** September 1998 to September 2000 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 100 patients. **Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Radiotherapy to internal mammary chain 5/59 (8.5%) Systemic treatment 3/59 (5.1%)

Authors	Intervention	Study Design	Study Population
Pijpers, Meijer, Hoekstra, Collet, Comans, Boom, van Diest & Teule, 1997. **Institution** Departments of Nuclear Medicine, Surgical Oncology, Pathology and Surgery and Academisch Zeikenhuis van de Vrije Universiteit, Amsterdam and Amstelveen Hospital, Amstelveen, the Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients with core biopsy proven breast cancer, without clinical evidence of axillary metastases, scheduled for lumpectomy or mastectomy and axillary clearance. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The day before surgery, patients were injected with 40 MBq Tc99m in 4 ml saline (3-80 nm; 77±12% < 30nm) in two to four depots in the axillary peritumoral hemisphere. Medial depots were not given as visualisation of parasternal drainage was reported to not have clinical consequences at present. Removal of sentinel lymph nodes Anterior and lateral views were obtained 2 hr and 18 hr post-injection using a LFOV dual-head gamma camera. Anatomical landmarks were marked on the skin with ink to allow for qualitative comparison between early and late imaging. Preoperatively, axillary focal accumulations were localised with a handheld collimated gamma probe. Surgery was performed 22 ± 2 hr after injection of the tracer. The operation field was checked for residual radioactivity following surgery. All radioactive lymph nodes were isolated from the surgical specimen using the gamma probe, followed by ex vivo measurement (10 sec) of their radioactivity. Parasternal nodes were not removed. The number and site of scinitigraphic foci were compared to lymph nodes detected with gamma probe. Pathology The SNs and remaining lymph nodes from the axillary specimen were cut in approximately 0.2 cm slices, fixed in 10% buffered formalin and embedded in paraffin. Four micron-thick sections were cut and stained with H&E.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 37 patients **Age** 58 ± 12 years **Type of surgery** Lumpectomy or mastectomy and ALND (2 patients refused ALND but biopsy on single radiolabelled node was performed). **Stage of disease** T1 (<20 mm) 14/37 (38%) T2 (20-40 mm) 23/37 (62%) **Tumour location** Not stated **Tumour location** UOQ 17/37 (46%) UIQ 6/37 (16%) LOQ 4/37 (11%) LIQ 3/37 (8%) Central 7/37 (19%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Rahusen, Meiher, Taet van Amerongen, Pijpers & van Diest, 2003. **Institution** Departments of Surgical Oncology, Radiology, Nuclear Medicine and Pathology, Vrihe Universiteit Medical Center, Amsterdam, The Netherlands. **Inclusion/exclusion criteria** Inclusions: patients with nonpalpable, mammographically suspect breast lesions. Almost all patients in this study were referred from the regional screening program. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection On the day before surgery, 20 to 80MBq of 99mTc-labelled albumin colloid (Nanocoll; Sorin Biomedica, Saluggia, Italy), was injected into the breast parenchyma around the tumour using either stereotactic or ultrasound guidance (initial set of patients). Later, subdermal or para-areolar radiocolloid injections were done in the quadrant of the tumour. Lymphoscintigraphy was performed after at least two hours, and up to 18 hours after radiocolloid injection. Approximately 5 minutes before incision, 0.5ml of 2.5% Patent Blue V (Guerbet, Aulnay-sous-Bois, France) was injected intradermally in the periareolar skin of the quadrant corresponding to the tumour. Removal of sentinel lymph nodes Dissection of the areolar fat was guided by a hand-held gamma probe (C-trak; Care Wise Medical Products, Morgan Hill, CA, USA; Navigator; Radiation Monitoring Devices, Watertown, MA, USA) and the sentinel node was identified as radioactive and/or blue. The open axilla was also palpated for enlarged nonsentinel nodes, which were sent separately to pathology. Pathology Lymph nodes <1cm were halved, and ≥1cm were lamellated in parts of approximately 0.5cm. All node pieces were fixed and paraffin embedded. If the initial paraffin sections were negative (by H&E), four skip sections were cut from each block and one section stained with H&E and one with CAM 5.2 (Becton Dickinson, San José, CA, USA) for immunohistochemistry, to detect micrometastases (metastases <2mm). In this way, 10 slides were systematically prepared from each block when the original H&E section was negative.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 67 patients **Age** Mean 61, range 33 to 84 years **Type of surgery** Not stated **Stage of disease** Mean 1.2, range 0.4 to 2.6cm (in patients with invasive malignancy. **Tumour histology** Invasive cancer: 51/67 (76.1%) DCIS: 8/67 (11.9%) No malignancy: 8/67 (11.9%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Ratanawichitrasin, Levy, Myles & Crowe, 1998. **Institution** Department of General Surgery, Cleveland Clinic Breast Center and Department of Anatomical Pathology, Cleveland Clinic Foundation, Cleveland, Ohio, USA. **Inclusion/exclusion criteria** Inclusions: breast cancer patients scheduled for ALND as part of their treatment. Patients with breast tumour either present or recently excised were included. Patients with intraductal, invasive ductal or invasive breast cancer were included regardless of tumour, nodes, metastasis staging. Exclusions: patients were excluded if they had previous ipsilateral axillary surgery or breast irradiation, preoperative chemotherapy for breast cancer or inflammatory cancer.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Patients were injected with 3-5 ml of 1% isosulfan blue (Lymphazurin, Ben Venue Labs, Bedford, OH) vital dye in approximately 0.5 ml quantities into the breast parenchyma surrounding the breast mass or around the prior breast biopsy site, using a 25-gauge needle. In cases of a previous biopsy and a long incision, injections were made on the axillary side of the incision. The injection site was gently compressed for a few minutes to enhance lymphatic uptake of the dye but with an effort to avoid potential dissemination of tumour cells. Removal of sentinel lymph nodes Within about 20 minutes of dye injection, but before mastectomy or ALND, an effort was made to identify blue-staining nodes for visuals inspection. The identification was done through a separate axillary incision for patients who were having an axillary dissection with or without partial mastectomy or through lateral aspect of the mastectomy incision for mastectomy patients. An attempt was made to identify a blue-staining lymphatic tract and trace it to a blue-staining node. Once identified, the blue noes were removed and submitted as separate specimens. SLNB was followed by standard Level I and II ALND. Pathology The nodes were divided, fixed, sectioned, stained with H&E and analysed.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** February to June 1997 **Operator details** All surgical procedures were performed by two experienced breast surgeons who did not have prior experience with this technique. Patients were advised that urine and faeces might be blue for 24 hours after isosulfan blue administration. **Outcome measures** Not applicable	**Sample size** 40 patients **Age** Median 57, range 30 to 78 years **Type of surgery** Modified radical mastectomy: 13/40 (33%) Lumpectomy or partial mastectomy plus ALND: 15/40 (38%) ALND alone: 12/40 (30%) **Stage of disease** Mean tumour size, 20±14, range 5 to 60 mm **Tumour histology** Not stated **Tumour location** UOQ: 17/40 (42.5%) UIQ: 8/40 (20%) LOQ: 7/40 (17.5%) LIQ: 1/40 (2.5%) Upper central: 3/40 (7.5%) Lower central: 2/40 (5%) Subareolar: 2/40 (5%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Rodier, Routiot, Mignotte, Janser, Bremond, David, Barlier, Ghnassia, Treilleux, Chassagne & Velten, 2000. **Institution** Department of Surgical Oncology, Paul Strauss Comprehensive Cancer Center, Strasbourg, France* and Léon Bérard Comprehensive Cancer Center, Lyon, France. **Inclusion/exclusion criteria** Inclusions: patients with invasive operable breast carcinoma (T0, T1, T2 < 3 cm). Exclusions: pregnancy, large tumours (T2 > 3 cm, T3 and T4), multicentric tumours and metastatic disease. Allergic patients were excluded to avoid patent blue anaphylactic reactions. Patients with previous breast tumour excision or axilla surgery, or who were treated by neoadjuvant chemotherapy or radiotherapy were also excluded from the study because of potential modification/transection of breast lymphatic vessels. Note: also reported in Rodier & Janser, 1997.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection All patients underwent an intradermal 2 ml patent blue dye (Guerbert, Aulnay-sous-Bois, France) injection in four peritumoral 0.5 ml aliquots at the palpable tumours (T1, T2 < 3 cm) or previously located tumour site (T0) immediately before surgery. Nonpalpable lesions (T0) were localised preoperatively by needle puncture with intramammary wire setting or by skin reference marks. Gentle circular motions of the breast were performed to improve dye axillary diffusion. A minimum 10 min rest was observed before starting tumour excision. [2 ml Blue Patent V was administered intradermally on the side of the palpable breast tumour facing the axillary nodal basin.]* Removal of sentinel lymph nodes The sequence of surgical procedure was tumour excision (conservative or radical) followed by sentinel node procedure, then followed by standard axillary (level I and II) clearance. Patients with conservative surgery had a separate transverse axillary incision below hair-bearing area. Care was taken to follow the stained lymphatic tracts until identification of the blue-stained SN. Pathology Harvested sentinel and non-sentinel nodes were submitted separately to the pathologist. Frozen sections were not routinely used. Each SN was grossly cut into 2- to 3-mm thick sections and embedded in paraffin. Both sentinel and non-sentinel nodes were stained with H&E. Multiple microscopic step sections were used in SNs free of metastasis.	Case series **Level of evidence** Level IV **Follow-up** Not stated. **Loss to follow-up** Not stated. **Study period** January 1996 to June 1997 **Operator details** All patients were operated on by four senior surgeons (JFR and JCJ in Strasbourg Cancer Center; HM and AB in Lyon Cancer Center) **Outcome measures** Not applicable	**Sample size** 73 patients (74 mapping procedures, 1 patient with bilateral breast cancer) **Age** Mean 59.5, range 39 to 80 years **Type of surgery** Conservative surgery: 60/74 (81.1%) Modified radical mastectomy: 14/74 (18.9%) **Stage of disease** Mean tumour size (diameter), 14.5, range 0 to 30mm cT0: 13/74 (17.6%) cT1: 47/74 (63.5%) cT2 (<3cm): 14/74 (18.9%) cN0: 70/74 (94.6%) pT1a: 5/74 (6.8%) pT1b: 13/74 (17.6%) pT1c: 34/74 (45.9%) pT2: 22/74 (29.7%) pN-: 47/74 (63.5%) **Tumour histology** Invasive ductal carcinoma: 62/74 (83.8%) Lobular carcinoma: 8/74 (10.8%) **Tumour location** Outer: 44/74 (59.5%) Inner: 17/74 (23.0%) Central/retroareolar: 13/74 (17.6%) **Receptor status** Oestrogen receptor positive: 56/71 (78.9%) Progesterone receptor positive: 54/71 (76.0%) **Menopausal status** Postmenopausal: 55/73 (75.3%) **Adjuvant therapy** 7/23 (30.4%) premenopausal patients with only blue-stained SN affected received adjuvant chemotherapy.

Authors	Intervention	Study Design	Study Population
Rönka, Krogerus, Leppänen, Smitten & Leidenius, 2002. **Institution** Breast Surgery Unit, Department of Pathology and Unit of Nuclear Medicine Maria Hospital, Helsinki University Hospital, Helsinki, Finland. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-labelled human albumin colloid (ALBU-RES99mTc albumin microcolloid Nycomed Amersham Sorin s.r.l. Saluggia, Italy or Nanocoll Sorin Biomedica diagnostics, Saluggia, Italy) was injected intratumourally in a volume of 0.2 ml (80-100 MBq). Albu-Res (particle size 0.2-3 μm) was used in 31 patients and Nanocoll (particle size < 80 nm) in 139 patients. The radioisotope injection was performed in palpation control in 133/172 (77.3%), in ultrasound control in 37/172 (21.5%) and after excisional biopsy in 2/172 (1.2%) cases. At least 5 minutes prior to incision, 1 ml of Patent Blue dye was injected intratumourally (Bleu Patenté V, Laboratoire Geurbet, Aulnay-sous-Bois, France). Removal of sentinel lymph nodes Lymphoscintigraphy was performed the day before surgery, four hours after tracer injection. The SNs were harvested using a gamma probe and by searching blue-stained lymphatic vessels and nodes. All radioactive and/or blue nodes in the axilla were harvested in the axilla. Pathology SNs were sent to pathology as separate samples labelled with site of origin. Fresh specimens were cleaned, measured, sliced into 1 – 1.5 mm-thick sections and mounted on iced OCT™. Touch preparations and frozen sections from 2 levels were made from these slices. These were stained with toluidine blue and viewed. The remaining tissue was fixed in phosphate-buffered 10% formalin, embedded in paraffin and sectioned stained with H&E and Cam 5.2 immunostain. When frozen section diagnosis was not required (SNs outside the axilla), the nodes were fixed directly into phosphate-buffered 10% formalin. After fixation the nodes were cleaned, cleaved and embedded wholly. H&E sections were made from 2 levels of each lymph node and cytokeratin immunostaining was done from 1 level. Axillary clearance was performed when the SN(s) in the axilla were involved, they were not identified, they were only blue without any radioactivity or if the tumour proved to be multifocal. It was attempted to retrieve SNs outside levels I-II of the axilla, when clearly visible in lymphoscintigraphy.	Case series (prospective) **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** May 30, 2000 to April 4, 2001 **Operator details** The Ethical Committee of Helsinki University Hospital approved the project plan. Written informed consent was obtained from each patient. **Outcome measures** Not applicable	**Sample size** 170 patients (172 mapping procedures, 2 patients with bilateral breast cancer) **Age** Median 57, range 28 to 86 years **Type of surgery** Conservative surgery or mastectomy, proportions not stated **Stage of disease** Median 16, range 4 to 45mm Stage I: 64/172 (37.2%) Stage II: 74/172 (43.0%) Stage III: 33/172 (19.2%) Not stated: 1/172 (0.6%) Tis: 6/63 (9.5%) T1: 12/63 (19.0%) T2: 44/63 (69.8%) T3: 0/63 (0%) T4: 1/63 (1.6%) Note: T stage data only provided for 63 tumours. **Tumour histology** Ductal carcinoma: 91/172 (52.9%) Lobular carcinoma: 56/172 (32.6%) Tubular carcinoma: 11/172 (6.4%) DCIS: 6/172 (3.5%) Other types: 8/172 (4.7%) **Tumour location** UOQ: 95/172 (55.2%) UIQ: 33/172 (19.2%) LOQ: 26/172 (15.1%) LIQ: 7/172 (4.1%) Central: 11/172 (6.4%) Right: 84/172 (48.8%) Left: 88/172 (51.2%) **Receptor status** Not stated **Menopausal status** Not stated

			Adjuvant therapy Not stated

Authors	Intervention	Study Design	Study Population
Sabel, Schott, Kleer, Merajver, Cimmino, Diehl, Hayes, Chang & Pierce, 2003. **Institution** Breast Oncology Program, Division on Medical Oncology and Departments of Pathology and Radiation Oncology University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; Division of Surgical Oncology, 3304 Cancer Center, Ann Arbor, Michigan, USA. **Inclusion/exclusion criteria** Inclusions: clinically node negative patients with clinical primary tumours 1.5cm or greater. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 99mTc-labelled sulphur colloid (3 to 4 mCi) was injected intradermally or perilesionally in combination with 3 to 5ml of Isosulfan Blue, injected peritumorally in four quadrants adjacent to the tumour. Removal of sentinel lymph nodes Lymph nodes with evidence of dye uptake or radioactive as detected by a hand-held gamma probe (Navigator; US Surgical, Norwalk, CT, USA) were labelled as sentinel nodes. Pathology Each sentinel node was cut along its longitudinal axis into sections of 1.5 to 2mm sections, fixed in formalin and embedded in paraffin. Each paraffin block was sectioned at three levels. No cytokeratin stains were performed. A standard level I and II axillary clearance was performed at definitive surgery for patients who had metastases to sentinel nodes.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** January 2001 to July 2002 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 25 patients (26 mapping procedures, 1 patient with bilateral breast cancer) **Age** Mean 45.13 ± 9, range 31 to 65 years **Type of surgery** Patients underwent sentinel lymph node biopsy before neoadjuvant chemotherapy. Once neoadjuvant chemotherapy was completed, the patients underwent definitive surgery. Mastectomy: 12/26 (46.2%) Lumpectomy: 14/26 (53.8%) **Stage of disease** Size prior to neoadjuvant chemotherapy, mean 3.0cm; size after neoadjuvant chemotherapy, mean 0.85cm. T1c: 5/25 (20.0%) T2: 20/25 (80.0%) **Tumour location** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Neoadjuvant therapy** Neoadjuvant chemotherapy was performed after sentinel lymph node biopsy. The average time between presentation at initiation of chemotherapy was 28 ± 11, range 9 to 52 days. A complete clinical response was achieved in 10/26 (38.5%) patients and 2/26 (7.7%) had a complete pathologic response. **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Sacchini, Borgen, Galimberti, Veronesi, Zurrida, Luini, Spaggiari, Cody & Veronesi, 2001. **Institution** Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Breast Department, European Institute of Oncology, Milan, Italy. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Not stated Removal of sentinel lymph nodes Access to the internal mammary nodes was obtained via the mastectomy incision or through the wide excision of the primary tumour. If this option was not available, a separate incision parallel to the stenum, extending for 3 to 4cm from the lateral sternal margin was considered, but no additional skin incision was required for this patient set. (More detail regarding the method of SLNB of the internal mammary nodes is discussed in the article). The procedure was performed under general anaesthesia in 137/142 (96.5%) and using local anaesthesia in 5/142 (3.5%). Pathology Not stated	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 142 patients **Age** Not stated **Type of surgery** Excision of internal mammary sentinel nodes. **Stage of disease** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Schrenk, Hatzl-Griesenhofer, Shamiyeh & Waynad, 2001. **Institution** Second Department of Surgery – Ludwig Boltzmann Institute for Surgical Laparoscopy and Department of Nuclear Medicine, Allgemein Offentliches Krankenhaus Linz, Linz, Austria. **Inclusion/exclusion criteria** Inclusions: cohort of a study who had a negative sentinel node and no axillary clearance. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Sentinel node mapping was achieved using vital blue dye alone or in combination with radiocolloid. Preoperative lymphoscintigraphy performed in all patients injected with radiocolloid. 40MBq Tc 99m Nanocoll® was injected into the parenchyma surrounding the tumour 18 hr preoperatively. 5ml isosulfan blue (1% Lymphazurin®, Ben Venue Labs., Inc., Bedford, OH, USA) was injected into the parenchyma surrounding the tumour. Non-palpable masses were injected under ultrasonic guidance and dye was injected into the cavity wall where the tumour had been excised. Removal of sentinel lymph nodes Sentinel nodes were identified intraoperatively using the hand-held Neoprobe 1000® (Neoprobe Corp., OH, USA). Sentinel nodes were identified as either being blue, when blue stained lymphatic channels led directly to the node, or hot. Pathology Interoperative frozen section was performed on 172/227 (76%) of successful sentinel node biopsies, the sentinel nodes bihalved and frozen section don from four to eight levels of one half. Where the node was tumour free, additional paraffin sections of 250 micrometres stained with H&E were done postoperatively. Negative sentinel nodes were subjected to cytokeratin IHC (antibody cocktail – CKKES, CKEMS; Immunostain®, Euro/DPC, Ltd., Gwynedd, UK) to cytokeratin in 2 to 4 levels. Cytokeratin stain regarded as positive when there was a cluster of positive-stained tumour cells. Micrometastases defined as a lymph node metastasis <2mm. In the 55/227 (24%) of successful sentinel node biopsies where frozen section was not performed, sentinel nodes were examined in paraffin sections of 250 micrometres stained with H&E, and in the case of a negative sentinel node, examined with IHC. Non-sentinel nodes were fixed in formalin, approximately four sections per lymph node and stained with H&E. No IHC was done in these nodes.	Case series **Level of evidence** Level IV **Follow-up** Median 22 months, range 4 to 48 **Loss to follow-up** Not stated **Study period** June 1996 to September 2000 **Operator details** All mapping procedures performed by the same surgeon (Schrenk). **Outcome measures** An anamnestic questionnaire regarding morbidity (arm pain, lymphoedema of the arm, arm and shoulder mobility, paraesthesia), clinical examination of the breast and regional lymph nodes were done every three months after surgery. Mammography, chest x-ray, ultrasonography of the liver and bone scans were performed annually or when indicated clinically.	**Sample size** 83 patients **Age** Mean 61.6, SD 12.8, range 35 to 84 years **Type of surgery** Quadrantectomy 66/83 (79.5%) Mastectomy 17/83 (20.5%) **Stage of disease** Mean tumour size, node negative 16.2, SD 8.1, range 1 to 40mm T1a 4/83 (4.8%) T1b 14/83 (16.9%) T1c 38/83 (45.8%) T2 17/83 (20.5%) Not stated 10/83 (12.0%) **Tumour histology** Ductal 69/83 (83.1%) Lobular 6/83 (7.2%) Papillary 5/83 (6.0%) Tubular 3/83 (3.6%) **Tumour location** UOQ 38/83 (45.8%) UIQ 10/83 (12.0%) LOQ 18/83 (21.7%) LIQ 7/83 (8.4%) Central 10/83 (12.0%) **Receptor status** Oestrogen receptor positive, progesterone receptor positive 57/83 (68.7%) Oestrogen receptor positive, progesterone receptor negative 15/83 (18.1%) Oestrogen receptor negative, progesterone receptor positive 1/83 (1.2%) Oestrogen receptor negative, progesterone receptor negative 10/83 (12.0%) **Menopausal status** Premenopausal 21/83 (25.3%) Postmenopausal 62/83 (74.7%)

			Adjuvant therapy Patients who had breast conserving surgery received 45Gy over 5 weeks to the breast with a boost to the tumour site, the axilla was excluded from the radiation field. Chemotherapy and hormonal therapy was used. 6/83 (7%) of patients refused any adjuvant treatment.

Authors	Intervention	Study Design	Study Population
Stradling, Aranha & Gabram, 2002. **Institution** Chicago College of Osteopathic Medicine of Midwestern University, Chicago, IL, USA and Department of Surgery, Loyola University Medical Center, Maywood, IL, USA. **Inclusion/exclusion criteria** Inclusions: consecutive patients. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Radiolabelled sulfur colloid Tc-99m injected in the periareolar region prior to surgery and 3 to 5cc 1% methylene blue dye injected into the deep parenchyma and intradermally around the tumour or biopsy cavity, followed by breast massage for 5min in the operating room. Removal of sentinel lymph nodes Not stated Pathology Not stated	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** September 19 2001 to November 18 2001 **Operator details** Retrospective review conducted from two surgeons lists. Radioactive colloid injected by Nuclear Medicine Department radiologists. **Outcome measures** Patients in whom developed superficial ulceration, intense erythematous lesion or a necrotic lesion were given sulfadiazine cream or gentamycin cream and were queried as outpatients regarding improvement of symptoms, lesion appearance and data were collected when adjuvant therapy was initiated.	**Sample size** 24 patients **Age** Not stated for all patients **Type of surgery** Appropriate surgery to remove the breast tumour or to obtain clear margins. **Stage of disease** Not stated for all patients **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Tanis, Nieweg, Valdés Olmos, Peterse, Rutgers, Hoefnagel & Kroon, 2002b. **Institution** Department of Surgery, Department of Nuclear Medicine and Department of Pathology, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The day before surgery, patients were injected with Tc99m (Amersham Cygne, Eindhoven, the Netherlands) into the tumour (0.2 ml mean volume; 104 MBq mean radioactive dose (range 42-159). The following day, 1 ml patent blue dye (Blue Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected into the tumour. Removal of sentinel lymph nodes A hot spot was considered to be a sentinel node if an afferent lymphatic channel was visualised, it was the first seen in a sequential pattern, it was the only one in a particular lymph node basin or when a combination of criteria were present. Intramammary, paramammary and interpectoral sentinel nodes were defined as interval nodes because of their location on the drainage route/internal mammary chain. The location of a sentinel node was marked on the skin. The sentinel node was identified as blue, radioactive or both and harvested after dissection of blue lymphatic vessels and detection of radioactivity with a gamma probe (Neoprobe®, Johnson & Johnson Medical, Hamburg, Germany). Internal mammary sentinel nodes were explored through a small transverse incision over the intercostal space concerned. After splitting the pectoral muscle fibres and dividing the intercostal muscles, radioactive lymph nodes were dissected from the internal mammary vessels and parietal pleura. "Sentinel nodes outside level I and II of the axilla were seen on the lymphoscintigraphy images in 147 patients and in an additional two patients intraoperatively using patent blue dye. Therefore the incidence was 27% (149 out of 549 patients)." "Management was modified in several respects in 26 out of 149 patients (17%), which compromises 5% of the whole sample population. Internal mammary chain irradiation was given to seven of the 149 patients (5%) which they would not have received if the prior guidelines had been followed. Internal mammary chain irradiation was not given to nine patients (6%) who otherwise would have received such treatment. Eight patients (5%) received adjuvant chemotherapy or hormone treatment only because of isolated non-axillary sentinel lymph node metastases. The finding of an extra-axillary sentinel node prevented axillary lymph node dissection in ten patients (7%) without a blue or radioactive lymph node in the axilla." Pathology Sentinel nodes were fixed in formalin, bisected, embedded in paraffin and cut at a minimum of six levels at 50 to 100µg intervals. Paraffin sections were stained with H&E and IHC (CAM 5.2, Becton Dickinson, San Jose, CA, USA).	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** January 1997 to July 2001 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 549 patients (555 mapping procedures, 6 patients with bilateral breast cancer) **Age** Mean 56, range 27 to 91 years **Type of surgery** Conservative surgery: 390/549 (71.0%) Mastectomy: 159/549 (29.0%) **Stage of disease** Mean tumour size, 19, range 2 to 80mm Tis: 12/549 (2.2%) T1: 455/549 (82.9%) T2: 90/549 (16.4%) T3: 4/549 (0.7%) **Tumour histology** DCIS: 12/549 (2.2%) Invasive: 537/549 (97.8%) **Tumour location** Inner/central: 211/555 (38.0%) Outer: 344/555 (62.0%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Radiotherapy to internal mammary chain: 10/549 (1.8%) Radiotherapy to axilla: 1/549 (0.2%) Tamoxifen: 7/549 (1.3%) Oophorectomy: 2/549 (0.4%) Chemotherapy: 2/549 (0.4%)

Authors	Intervention	Study Design	Study Population
Tsugawa, Noguchi, Miwa, Bando, Yokoyama, Nakajima, Michigishi, Tonami, Minato & Nonomura, 2000. **Institution** Department of Surgery, Operation Center, Department of Nuclear Medicine and Division of Pathology, Kanazawa University Hospital, Kanazawa University School of Medicine, Takara-machi, Kanazawa, Japan. **Inclusion/exclusion criteria** Inclusions: Tis (carcinoma in situ), clinical stage I or II breast cancer (primary operable breast cancer). Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 3 mCi of ^{99m}Tc-labelled HSA (Dai-ichi Radioisotope Laboratory Co Ltd, Tokyo, Japan) in a volume of 0.3 ml was injected into the subdermal tissue above the primary tumour or biopsy cavity. Patients were scheduled to undergo preoperative lymphoscintigraphy. After general anaesthesia. 4 ml of 1% patent blue dye (CI 42045, Wako Pure Chemical Industries, Ltd, Osaka, Japan) was injected with a 25-gauge needle into the peritumoral area 5 to 15 min prior to the surgical procedure. The injections were placed 12, 3, 6 and 9 o'clock positions surrounding the breast tumour and at the same depth as the tumour. If the primary tumour had been excised, Tc 99m-HSA and blue dye were injected in the walls of the biopsy cavity and surrounding tissues. Removal of sentinel lymph nodes Ten minutes and 1 hr after tracer injection lymphoscintigraphy was performed by a gamma camera (ECAM, Siemens-Toshiba, Nasu, Japan), and one or more hot spots were assumed to be SNs and were marked on the skin. Thirty min and 2 hr after tracer injection patients came to operating room. A hand-held gamma probe was used to assist in SN detection. Two-commercially available systems for radio-guided surgery, C-Trak System (Care-Wise Medical Product, Morgan Hill, CA, USA) and Navigator System (RMD Inc, Watertown, MA USA) were used. The probe was used prior to incision to identify the area of greatest activity in the axilla. Dissection was performed through the axillary or mastectomy incision to identify blue-stained afferent lymphatic vessels and nodes. The dye-filled tract was dissected to the first blue node. The gamma probe was used to confirm the location of SN and guide dissection. SN was defined as any blue and/or hot node with 10:1 *ex vivo* gamma probe ratio of SN to non-SN. After the SN was excised, a gamma probe was put in the axilla to confirm that there was no remaining radioactive node. After SN biopsy using two mapping procedures, a complete ALND (level I-III) was performed conventionally with management of the primary lesion. Internal mammary lymph node biopsy was performed in patients with internal mammary radioactive foci. Pathology Resected breast tissue was fixed in 10% formalin, embedded in paraffin and examined by H&E on permanent section. SNs were examined with H&E on permanent sections. At least three sections were obtained from each SN at different levels (100-500 μm apart). If no tumour was identified on H& E, another section was stained with IHC (MAS 494, Harlan Sera-Lab Ltd, Loughborough, UK). ALND and MN specimens were processed by routine surgical pathological techniques and stained with H&E.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** March 1998 to April 1999 **Operator details** After informed consent, clinical staging was performed according to the Clinical Classification of Breast Cancer proposed by the Japanese Breast Cancer Society. **Outcome measures** Not applicable	**Sample size** 48 patients **Age** Mean 52, range 30 to 86 years **Type of surgery** Modified radical mastectomy: 18/48 (37.5%) Conservative surgery: 30/48 (62.5%) **Stage of disease** Tumour size, 22 ± 12 mm T0: 1/48 (2.1%) T1: 24/48 (50.0%) T2: 23/48 (47.9%) N0/N1a: 38/48 (79.2%) N1b: 10/48 (20.8%) **Tumour histology** Non-invasive ductal carcinoma: 4/48 (8.3%) Invasive ductal carcinoma: 40/48 (83.3%) Other invasive carcinoma: 4/48 (8.3%) **Tumour location** Lateral: 30/48 (62.5%) Medial: 18/48 (37.5%) **Receptor status** Not stated **Menopausal status** Postmenopausal: 21/48 (43.8%) **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Uğur, Bozkurt, Sayek, Gedíkoğlu, Baykal, Hamaloğlu, Etíkan, Konan & Erbaş, 2003. **Institution** Departments of Nuclear Medicine, Surgery, Pathology and Biostatistics, Hacettepe University Faculty of Medicine, Ankara-Turkey. **Inclusion/exclusion criteria** Inclusions: patients with unifocal primary invasive breast cancer with clinically negative axilla scheduled for mastectomy or lumpectomy and axillary clearance. Exclusions: patients with multicentric primary breast cancer or clinically positive regional lymph nodes.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-labelled rhenium sulphide (Nanocolloid; CIS biointernational, France) or ^{99m}Tc-labelled tin (Amerscan Hepatate II Agent, Nycomed Amersham plc, UK) was injected intradermally in the same quadrant as the tumour, 2 to 12 hours before operation. Lymphoscintigraphy was performed immediately following radiocolloid injection. After induction of general anaesthesia, 5ml of 1% isosulfan blue was injected and gentle massage was applied for a few minutes. Removal of sentinel lymph nodes Intraoperative localisation was performed using a hand-held gamma probe (Neoprobe 2000; Neoprobe corporation, Dublin, OH, USA). Sentinel lymph node biopsy was performed through a standard anteroposterior incision placed in the lower axillary hair-bearing skin, as routinely performed in axillary clearance. The gamma probe guided the dissection and radioactive node(s) that exhibited *in vivo* counts of at least three times background and *ex vivo* counts of at least 10 times background were accepted as sentinel nodes. Pathology Detailed microscopic examination of three sections from each bihalved sentinel nodes (and one section from each nonsentinel node) was performed. In addition to H&E staining, cytokeratin and epithelial membrane antigen (EMA) immunohistochemistry was also applied to the sentinel nodes. Routine axillary dissection through levels I, II and/or III was completed after mastectomy.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not stated **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 28 patients (27 female:1 male, 29 mapping procedures, 1 patient with bilateral breast cancer) **Age** Individual ages were stated, range 25 to 74 years **Type of surgery** Not stated **Stage of disease** Individual sizes were stated, range <2mm (DCIS) to 6cm. T1: 16/28 (57.1%) T2: 6/28 (21.4%) T3: 3/28 (10.7%) DCIS: 3/28 (10.7%) **Tumour histology** Infiltrating ductal: 18/28 (64.3%)* Infiltrating lobular: 1/28 (3.6%) Mixed infiltrating ductal/lobular: 3/28 (10.7%) Mucinous: 1/28 (3.6%) Intraductal carcinoma: 2/28 (7.1%) DCIS/intraductal: 3/28 (10.7%) * Including two microinvasive ductal carcinoma. **Tumour location** UOQ: 15/29 (51.7%) UIQ: 2/29 (6.9%) LOQ: 6/29 (20.7%) Central: 6/29 (20.7%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
van Berlo, Hess, Nijhuis, Leys, Gerritsen and Schapers, 2003. **Institution** Departments of Surgery, Nuclear Medicine and Pathology, VieCuri Medical Center, Venlo, The Netherlands. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-nanocolloid (1mCi) was injected 18 hours before operation (intradermally until January 2001, later half intradermally, half peritumourally). Lymphoscintigraphy was performed on the day of surgery, in two planes to mark the sentinel node(s). Five minutes before incision, 0.5cc of patent blue (Blue Patenté V; Laboratooire Guebet, Aulnay-sous-Bois, France) was intradermally injected. Removal of sentinel lymph nodes From July 1997 until December 1998, AC was performed in 58 patients (56 women) up to level III after the sentinel node was found and presented for pathological examination. From January 1999 onwards, AC was only performed in patients with positive sentinel nodes. All these procedures were completed under general anaesthesia. From September 2000 until February 2002, 162 patients (161 women) with proven breast cancer, but without evidence of regional or distant metastases, were operated under local anaesthetic, without sedation, in the out-patient department (Prilocaïn 1% (15cc; Astra Pharmaceutic B.V., Zoetermeer, The Netherlands) was infiltrated into the axilla to obtain local anaesthesia). The sentinel node was identified intraoperatively using the blue colour and a hand-held gamma probe (Neoprobe 1000, until February 2000, later Neoprobe 2000; Neoprobe Corporation, Dublin, Ohio, USA) and palpation. Pathology Histopathological examination including immunohistochemistry was performed.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** July 1997 to February 2002 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 290 (287 female:3 male) **Age** Not stated **Type of surgery** Breast-conserving: 216/290 (74.5%) Mastectomy: 74/290 (25.5%) **Stage of disease** Tis: 3/290 (1%) T1: 209/290 (72.1%) T2: 65/290 (22.4%) T3: 11/290 (3.8%) T4: 2/290 (0.7%) **Tumour histology** Ductal: 234/290 (80.7%) Lobular: 31/290 (10.7%) Other: 25/290 (8.6%) **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
van der Ent, Kengan, van der Pol, Povel, Stroeken & Hoofwijk, 2001. **Institution** Department of Surgery and Nuclear Medicine, Maaslandzieken-huis Sittard, The Netherlands. **Inclusion/exclusion criteria** Inclusions: consecutive patients with clinically node-negative operable primary breast cancer. Exclusions: pregnant women and those with T4 tumours. Note: also reported in van der Ent, Kengen, van der Pol & Hoofwijk, 1999.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The day before surgery, in the late afternoon, 10mCi (370 MBq) Tc 99m (Nanocoll, Nycomed Amersham Sorin, Saluggia, Italy; Nanocoll, SolcoNuclear, Switzerland*) in 4 ml saline was injected peritumorally in 3-4 depots around the tumour. If a previous excisional biopsy had been performed, the tracer was injected into the breast tissue adjacent the biopsy cavity, avoiding the biopsy cavity itself. The following morning (mean 16 hr post-injection), lymphoscintigraphy was performed. After induction of general anaesthesia, 10 to 15 minutes before the incision, 0.8 to 1 ml patent blue V (Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected intradermally above the tumour or alongside the scar of the excisional biopsy. [After induction of general anaesthesia, 1-2 ml patent blue V was injected peritulorally in the first 12 cases. However, a blue axillary SN was found in only two patients. Thereafter, 0.5-0.8 ml blue dye was injected intradermally above the tumour or alongside the scar of the excisional biopsy.*] Removal of sentinel lymph nodes Attempts were made to harvest both the axillary and nonaxillary SNs. Intraoperative identification of the SNs was based on blue dye mapping and gamma probe detection (RMD 10 mm, Radiation Monitoring Devices, Inc, Watertown, MA, USA). Interference from primary site radioactivity of medial tumours, impeding internal mammary SN identification, was managed by using an additionally collimated gamma probe and by narrowing the energy window of the probe. Despite these measures, interference occasionally led to failure in sampling a parasternal SN. Post-operative chest radiography was obtained after internal mammary node biopsy to exclude pneumothorax. In Phase 1 (n=137) SN biopsy was followed by ALND, but after SN technique validation, Phase 2 ALND was performed in cases of +ve axillary SN tumours or after unsuccessful SN procedure. [Axillary biopsy was perfomed prior to lumpectomy in cases of breast-conserving surgery and in conjunction with mastectomy in cases of ablative surgery. The gamma probe was used *in vivo* to identify SN and blue staining was regarded as complementary in harvesting possible SNs. When the radioactive SNs were not blue-stained, generally no effort was made to localise additional blue lymph nodes. In absence of radioactive SNs, blue dye mapping alone was used to identify the SN. After removal of the SN, radioactivity was measured *ex vivo* in each SN and the remaining axillary tissue was then re-eamined for additional SNs with the gamma proble. If the remaining activity was less than 10% of the most active SN, no additional SNs were believed to exist. After completing the SN biopsy, ALND was performed. Internal mammary SN biopsy was attempted in cases which lymphoscintigraphy confirmed the presence of parasternal sentinel nodes. Patients who underwent modified radical mastectomy, internal mammary sampling was feasible using the same incision.*] Pathology Pathological examination consisted of routine H&E. Serial sectioning and IHC were also used whenever initial H&E did not reveal metastatic involvement in the presence of metastases in the remaining ALND specimen.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** April 1997 to February 2000. **Operator details** Not stated **Outcome measures** Not applicable.	**Sample size** 256 patients (255 female:1 male) **Age** Not stated **Type of surgery** Not stated **Stage of disease** T1 119/256 (46.5%) T2 117/256 (45.7%) T3 20/256 (7.8%) **Tumour histology** Not stated **Tumour location** UOQ 116/256 (45.3%) UIQ 58/256 (22.7%) LOQ 36/256 (14.1%) LIQ 26/256 (10.2%) Central 20/256 (7.8%) **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Walker, Hussain & Humphrey, 2002. **Institution** Rochdale Breast Unit, Birch Hospital, Rochdale, UK. **Inclusion/exclusion criteria** Inclusions: none stated Exclusions: features considered contraindications to the procedure were a heavy axillary tumour burden as assessed clinically, previous axillary surgery, multifocal disease and therapeutic localisation biopsy.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection First 25 patients, 1-2 ml blue dye (patent blue V) was injected around the tumour, into the adjacent subcutaneous tissues, and intradermally, after induction of general anaesthesia. Lymphatic uptake was encouraged by gentle massage of the area. Subsequent technique modification resulted in omittance of the intradermal injection to reduce interval from dye injection to node identification to approximately 10 min. Removal of sentinel lymph nodes SN excision with subsequent axillary sampling. The breast was approached surgically first, followed by exploration of the axilla. This gave an injection to node time of approximately 25 min. Initial experience suggested the technique resulted in considerable contamination of operative fields, and it was not uncommon to find more than one blue-stained node. The technique was therefore modified (as mentioned above) to explore the axilla first via a separate curvilinear incision. Following excision of the SN (or if the node could not be identified), a formal four-node sampling was carried out. Pathology The pathological status of the SN was compared with that of the axilla using histological examination of paraffin-embedded tissue.	Case series **Level of evidence** Level IV **Follow-up** Not stated **Loss to follow-up** Not stated **Study period** November 1998 to August 2001 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 122 patients **Age** Mean 56, range 28 to 82 years **Type of surgery** Mastectomy: 2/122 (1.6%) **Stage of disease** Grade 1: 29/116 (25.0%) Grade 2: 52/116 (44.8%) Grade 3: 35/116 (30.2%) <20mm: 49/122 (40.2%) 20-30 mm: 67/122 (54.9%) >30 mm: 5/122 (4.1%) >35 mm: 0/122 (0.0%) Note: it was impossible to assess size of lesion in one case. **Tumour histology** Infiltrating ductal carcinoma: 93/122 (76.2%) Infiltrating lobular carcinoma: 16/122 (13.1%) Mucinous carcinoma: 2/122 (1.6%) Papillary tumours: 2/122 (1.6%) DCIS with microinvasion: 1/122 (0.8%) **Tumour location** Not stated for all patients. **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Yong, Wong, Lee, Soo, Tan & Goh, 2003. **Institution** Departments of Surgery, Pathology and Nuclear Medicine, Singapore General Hospital, Singapore. **Inclusion/exclusion criteria** Inclusions: patients with stage I and II breast cancer and non-palpable axillary nodes, including those with previous excision biopsy. Exclusions: pregnant women, those with previous axillary surgery and women with advanced breast cancer with enlarged axillary nodes.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Unfiltered ^{99m}Tc-labelled tin colloid (prepared by the Department of Nuclear Medicine, Singapore General Hospital), particle size range 200 to 800nm, injected peritumorally into the breast parenchyma in aliquots of 0.5 to 1.0ml (total of 2.0ml with an activity of 5mCi) on the side of the tumour facing the axilla and also on the two adjacent sides of the tumour. For patients who had a prior excisional biopsy, the radiocolloid was injected intraparenchymally into the area around the cavity guided by the scar. Radiocolloid injection was performed in the morning prior to surgery (2 to 6 hours before surgery). Lymphoscintigraphy was not performed. Approximately 2.0ml of 1% patent blue dye was injected just before general anaesthesia. The dye was injected in small aliquots around the tumour or biopsy cavity. The breast was massaged firmly for approximately five minutes. Removal of sentinel lymph nodes The sentinel node was localised with with aid of either the blue dye, the radioactive tracer or both, and was defined as a node that was stained blue and/or 'hot' where hot was at least 10times or more of background as measured by a hand-held gamma probe (C-trak; Care Wise Medical Products Corporation, Morgan Hill, CA, USA). Pathology All sentinel nodes were bisected and each half sectioned and examined with H&E. IHC was not performed. Axillary lymph nodes were examined in a similar way. A standard axillary dissection (level I and II) was subsequently performed.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** August 1996 to December 1998 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 312 patients **Age** Mean 53, range 28 to 83 years **Type of surgery** Not stated **Stage of disease** Mean 2.6, range 0.2 to 9.0cm Not stated except that 5 patients had tumours larger than 5 cm (T3) **Tumour histology** Invasive lobular 6% DCIS 88% Other (including mucinous and papillary carcinoma) 6% **Tumour location** Medial 16% Central 43% Lateral 41% **Receptor status** Not stated **Menopausal status** Premenopausal 51% Postmenopausal 49% **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Yu, Hsu, Liu, Sheu, Li, & Chao, 2002. **Institution** Department of Surgery, Division of General Surgery, Department of Radiology, Department of Pathology and Department of Medicine, Division of Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. **Inclusion/exclusion criteria** Inclusions: patients either with tumour smaller than 3 cm or those without clinically palpable tumour were evaluated. None of the patients had palpable axillary nodes by preoperative assessment. Exclusions: patients with prior breast operation, axillary surgery, axillary radiation therapy or preoperative adjuvant chemotherapy were excluded from the study.	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Under general anaesthesia, 5 ml of methylene blue dye (Rise Sun Trading Co., Taiwan) was injected into the peritumour breast parenchyma with a 25-gauge needle. If the primary tumour had been previously excised, the dye was injected into the wall of the biopsy cavity and surrounding breast parenchyma along the incision line under the guidance of ultrasonography. Removal of sentinel lymph nodes The interval between dye injection and axillary incision was approximately 5 minutes. A transverse incision (about 2 cm) was made just below the hair-bearing region of the axilla. Blunt dissection was performed until a dye-filled lymphatic tract or blue-stained node was identified. The dye-filled tract was traced to the first blue node. We followed the dye-filled lymphatic tract proximally to the tail of the breast, to ensure the blue-stained node was the SN. After the SN was identified, it was carefully excised. Pathology Every node greater than 2 mm was grossly sectioned and all nodal tissues were submitted for paraffin embedding and histologic examination using H&E. IHC for cytokeratin (DAKO, Denmark) was performed as indicated. Four histologic sections of each SN were examined. An experienced histopathologist examined at least two sections of other nodes. Prior to submitting SN for histopathologic examination, air-dried touch imprints for cytologic examination was prepared. Four slides, each with two impressions were prepared. Two slides were stained with Quick-Diff and two with IHC techniques for cytokeratin and for epithelial membrane antigen (DAKO, Denmark). ALND performed including levels I and II, Rotter's node and occasionally level III. If the SN was not identified, complete ALND was performed.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** October 1998 to December 2000 **Operator details** All operations were performed by a single surgeon (Yu). **Outcome measures** Not applicable	**Sample size** 218 patients (221 mapping procedures, 3 patients with bilateral breast cancer) **Age** Mean 46, range 26 to 82 years **Type of surgery** Modified radical mastectomy: 154/221 (69.7%) Quadrantectomy (conservative surgery): 67/221 (30.3%) **Stage of disease** ≤ 1 cm: 11/186 (5.9%) 1-2 cm: 88/186 (47.3%) 2-3 cm: 87/186 (46.8%) **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Zhang, Shen, Lamichhane, Liu, Wu, Shao & Shen, 2003. **Institution** Departments of Breast Surgery, Cancer Hospital/Institute, Fu Dan University, Shanghai. **Inclusion/exclusion criteria** Inclusions: breast cancer patients, clinically T1-2, N0. Exclusions: none stated	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The first 72 patients had 1 to 2mCi of unfiltered 99mTc-labelled sulphur colloid, in 3 to 5ml, injected into the breast tissue surrounding the primary tumour or biopsy site at the 3, 6, 9 and 12 o'clock positions. For the last 23 patients, the 3 to 4ml of the radiocolloid was injected subdermally at one point. Lymphoscintigraphy was performed before surgery. Removal of sentinel lymph nodes A hand-held gamma probe (Capintec Gammed IV; Capintec Inc., NJ< USA) was used to detect radioactivity. Sentinel lymph nodes biopsy was performed after the dissection of skin flaps, and was guided by the gamma probe. A hot spot was defined as 25 counts per second or greater. After resection, the activity of the axilla should be <10% of the the most radioactive node. Pathology Sentinel nodes were fixed in formalin, bisected and embedded. One or two sections obtained from the central cross section from each block was stained with H&E. If the sentinel node was negative by H&E, a further six sections were taken and two were stained for cytokeratin and one with H&E. Positive IHC findings were verified by H&E staining of the same level. Standard axillary dissection was performed after sentinel lymph node biopsy.	Case series **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** May 2000 to December 2001 **Operator details** Not stated **Outcome measures** Not applicable	**Sample size** 95 patients **Age** Mean 51.9 ± 10.8, range 25 to 86 years **Type of surgery** MRM: 75/95 (78.9%) Radical mastectomy: 11/95 (11.6%) Breast conserving surgery: 9/95 (9.5%) **Stage of disease** T1 to T2 <2cm: 34/95 (35.8%) 2 to 3cm: 31/95 (32.6%) >3cm: 19/95 (20.0%) (After excision): 11/95 (11.6%) **Tumour histology** Infiltrating ductal: 80/95 (84.2%) DCIS with early invasion: 4/95 (4.2%) Infiltrating lobular: 4/95 (4.2%) Mucinous: 3/95 (3.2%) Medullary: 3/95 (3.2%) Paget's disease and Intraductal carcinoma: 1/95 (1.1%) **Tumour location** UOQ: 51/95 (53.7%) UIQ: 15/95 (15.8%) LOQ: 16/95 (16.8%) LIQ: 9/95 (9.5%) Subareolar: 4/95 (4.2%) **Receptor status** Not stated **Menopausal status** Premenopausal: 50/95 (52.6%) Postmenopausal: 45/95 (47.4%) **Adjuvant therapy** Not stated

Table I.4 Case reports – Safety and effectiveness

Authors	Intervention	Study Design	Study Population
Cimmino, Brown, Szocik, Pass, Moline, De & Domino, 2001. **Institution** Departments of Surgery, Anesthesiology, and Pharmacology, University of Michigan Medical School and University hospital, Ann Arbor, Michigan, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Case 1: Injection of 3ml of isosulfan blue dye (1% Lymphazurin) intraparenchymally around the old biopsy site. Case 2: Injection of 5ml of isosulfan blue dye (1% Lymphazurin) subcutaneously near the previous biopsy site. Case 3: Injection of 5ml of isosulfan blue dye (1% Lymphazurin) subcutaneously near the previous biopsy site. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 50 years Case 2: 47 years Case 3: 47 years **Type of surgery** Case 1: Not stated Case 2: Breast conserving lumpectomy Case 3: Breast conserving lumpectomy **Stage of disease** Not stated **Tumour histology** Case 1: Invasive lobular carcinoma Case 2: Not stated Case 3: Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Crivellaro, Senna, Dama, Bonadonna & Passalacqua, 2003. **Institution** Allergy Service, Verona General Hospital; Allergy and Respiratory Diseases, Department of Internal Medicine, Genoa University, Italy. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Patent blue dye (1ml; 2.5% aqueous solution) was injected. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 54 years **Type of surgery** Mastectomy **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Efron, Knudsen, Hirshorn & Copeland, 2002. **Institution**Departments of Surgery and Anesthesia, Shands Hospital, University of Florida, Gainesville, Florida, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	Sentinel Lymph Node Biopsy Radioactive colloid and/or dye injection Preoperative lymphoscintigram (dermal and intraparenchymal injections) on the day before surgery. Attempted segmental mastectomy with SLNB and possible axillary dissection. Weak identification of radioactivity in left axilla and it was decided that the patient should undergo SN identification with isosulfan blue dye. Patient received 1g of preoperative cephalexin 1hr prior to induction of anaesthesia (laryngeal mask air way and anaesthesia with propofol and forane). Isosulfan blue (5ml) was injected intraparenchymally and manually massaged for 5min. Removal of sentinel lymph nodes Not applicable. Pathology Not applicable.	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 54 years **Type of surgery** Attempted segmental mastectomy **Stage of disease** 3.5cm **Tumour histology** Infiltrating lobular carcinoma **Tumour location** Left breast, quadrant not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Galatius, Holtveg & Følsgård, 2003. **Institution**Brystkirurgisk Klinik, Horsholm Sygehus, Horsholm, Denmark. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Case 1: 0.5ml of patent blue dye was injected intraparenchymally adjacent to the tumour. Case 2: 0.75ml of patent blue dye was injected intraparenchymally adjacent to the tumour. Case 3: 0.75ml of patent blue dye was injected intraparenchymally adjacent to the tumour. Case 4: not stated Removal of sentinel lymph nodes Not stated Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 79 years Case 2: 65 years Case 3: 46 years Case 4: not stated **Type of surgery** Case 1: mastectomy Case 2: mastectomy Case 3: mastectomy Case 4: not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Giménez, Botella-Estrada, Hernandez, Carbonell, Martinez, Guillen & Vazquez, 2001. **Institution** Departments of Surgery, Dermatology, Pharmacy and Anesthesia, Institute Valenciano de Oncologia and Department of Allergology, Hospital Universitario La Fe, Valencia, Spain. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	Sentinel Lymph Node Biopsy Radioactive colloid and/or dye injection Case 1: Unfiltered ^{99m}Tc-labelled sulphur colloid injected around the tumours 18 hours preop.. Antibiotic prophylaxis (ceftriaxone IV) and sedation (midazolam IV) were given immediately before operation. 20 minutes before the operation, 2ml 1% isosulphan blue (Lymphzurin®, Ben Venue Labs Inc, Bedford, OH, USA) was injected around the tumour in each breast. Anaesthesia was induced with fentanyl hydrochloride, propofol and rocuronium and maintained with oxygen, nitrous oxide and isofluorane. Case 2: Preoperative lymphoscintigraphy, antibiotic prophylaxis, induction of anaesthesia and injection of isosulphan blue was the same as for Case 1. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 48 years Case 2: 60 years **Type of surgery** Case 1: Scheduled for bilateral lumpectomy and axillary lymphadendectomy Case 2: Listed for wide excision and SLNB followed by AC. **Stage of disease** Not stated **Tumour histology** Case 1: Bilateral ductal carcinoma Case 2: Infiltrating ductal carcinoma **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Kuerer, Hunt, Singletary & Ames, 2001a. **Institution** University of Texas M.D. Anderson Cancer Center, Houston, TX, USA **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 5ml 1% isosulfan blue dye around the lumpectomy site Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 75 years **Type of surgery** Lumpectomy (5 weeks prior to SLNB) **Stage of disease** 1.4cm **Tumour histology** Invasive ductal cancer **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Kuerer, Wayne & Ross, 2001b. **Institution** University of Texas M.D. Anderson Cancer Center, Houston, TX, USA **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Filtered technetium ^{99m}Tc-labelled sulphur colloid into biopsy cavity wall preoperatively demonstrated primary left axillary lymphatic drainage. The patient received ampicillin, propofol and midazolam before surgery. Induction of anaesthesia with propofol and sufentanil and paralysis with rocuronium. 5ml of 1% isosulfan blue was injected and the breast gently massaged. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 52 years **Type of surgery** Prior excision, revealing positive margins, mammography revealed residual microcalcifications. Needle-localized segmented mastectomy, lymphatic mapping with SLNB and synchronous bilateral reduction mammoplasty were planned. **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Laurie, Khan, Gruchalla & Peters, 2002. **Institution** The University of Texas Southwestern Medical Center, Department of Internal Medicine, Division of Allergy and Immunology Dallas, TX, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Case 1: Subcutaneous injection of 5ml isosulfan blue. Case 2: Not stated Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 60 years Case 2: 62 years **Type of surgery** Case 1: (Underwent SLNB and partial mastectomy without the use of isosulfan blue 2 days after positive skin test) Case 2: (Underwent bilateral SLNB and bilateral partial mastectomies without the use of isosulfan blue) **Stage of disease** Case 1: Stage II carcinoma Case 2: Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Lyew, Gamblin & Ayoub, 2000. **Institution** Department of Anesthesiology, Mercer University School of Medicine, Macon, GA, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection 1mCi ^{99m}Tc-labelled sulfur colloid injected near the lump 2hours prior to surgery. 5ml of isosulfan blue (1% Lymphazurin; Ben Venue Labs., Bedford, OH, USA) was injected in 4 quadrants around the mass, after induction of anaesthesia. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 48 years **Type of surgery** Excision of carcinoma **Stage of disease** Not stated **Stage of disease** Ductal carcinoma **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Mullan, Deacock, Quiney & Kissin, 2001. **Institution** Department of Surgery; Department of Immunology; Department of Anaesthesia, Royal Surrey County Hospital, Guildford, Surrey, UK. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Case 1: Lymphoscintigraphy with 40mBq of ^{99m}Tc-labelled human albumin colloid particles (Nycomed, Amersham) the day prior to surgery. Shortly after anaesthetic induction, 5ml of patent blue V dye (Guerbet Laboratories, Milton Keynes, 2ml of 2.5% solution diluted to 5ml with normal saline) was injected peritumorally. The sentinel node that was blue and hot on gamma scanning with the Navigator® probe (Radiation devices, MA, USA) was excised. Case 2: Underwent lymphatic mapping as described for Case 1. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 67 years Case 2: 47 years **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Quiney, Kissin & Tytler, 2003. **Institution** Guildford, UK. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Peritumoral injection of Patent Blue V (Laboratoure Guerbet, Aulnay-Sous-Bois, France) dye. Removal of sentinel lymph nodes Not applicable. Pathology Not applicable.	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not applicable **Outcome measures** Not applicable	**Age** Not stated **Type of surgery** Not stated **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Sadiq, Burns, Taber, Damitz & Ollila, 2001. **Institution** Department of Surgery, University of North Carolina Hospitals, Chapel Hill, NC, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Case 1: Preoperative lymphoscintigraphy with radiolabeled sulfur colloid followed by segmental mastectomy and lymphatic mapping/sentinel lymphadenectomy under general anaesthesia. Intraparenchymal peritumoral injection of 1% isosulfan blue (2ml). Case 2: Preoperative lymphoscintigraphy with radiolabeled sulfur colloid followed by mastectomy and lymphatic mapping/sentinel lymphadenectomy under general anaesthesia with planned immediate transverse rectus abdominis myocutaneous flap reconstruction Intraparenchymal peritumoral injection of 1% isosulfan blue (2ml). Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** Case 1: 52 years Case 2: 57 years **Type of surgery** Case 1: segmental mastectomy Case 2: mastectomy with planned immediate transverse rectus abdominis myocutaneous flap reconstruction **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Salvat, Margonari & Hardelin, 1999. **Institution** Department of Obstetrics and Gynaecology; Department of Anaesthesia and Resuscitation Intensive Care; and Department of Pharmacy; Léman, Thonon, France. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection Intraoperative subdermal injection of 2 cc of 2.5% solution (Patent Blue V®) given 1 cm from the healed tumoural bed. Reflux at the level of the tumourectomy scar led operators to inject a further 2 cc, for a total of 4 cc. Mammary massage given for 10 minutes. Removal of sentinel lymph nodes Surgical axillary clearance of a malignant tumour. Sentinel node easily identified after a transverse axillary incision and identification of the principle collector. Clearance carried out without local incident. Pathology Not applicable	Case report **Level of evidence** IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 56 years **Type of surgery** Tumourectomy followed by axillary clearance one week later. **Stage of disease** T1 **Tumour histology** Not stated **Tumour location** Left breast **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** No medical treatment given prior to surgery. Post-surgery treatment not stated

Authors	Intervention	Study Design	Study Population
Sprung, Tully & Ziser, 2003. **Institution** Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA; Rambam Medical Center, Haifa, Israel. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection The surgeon subcutaneously injected 4 ml of 1% isosulfan blue. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 53 years **Type of surgery** Excision of breast carcinoma **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Not stated **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Stefanutto, Shapiro & Wright, 2002. **Institution** San Francisco, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection ^{99m}Tc-labelled sulphur colloid was injected, and lymphoscintigraphy performed, prior to transferral to the operating theatre. Anaesthesia induced using 150mg fentanyl, 120mg propofol and 40mg rocuronium. Uneventful anaesthesia continued for 50 min during initial stages of the surgery. After 50 min, 3ml isosulfan blue (Hirsch Industries Inc., Richmond, VA, USA) was injected subcutaneously around the tumour. Removal of sentinel lymph nodes Not applicable Pathology Not applicable	Case report **Level of evidence** Level IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 50 years **Type of surgery** Lumpectomy **Stage of disease** Not stated **Tumour histology** Not stated **Tumour location** Left breast, location not stated. **Receptor status** Not stated. **Menopausal status** Not stated. **Adjuvant therapy** Not stated

Authors	Intervention	Study Design	Study Population
Wear, Karsif & Turner, 2003. **Institution** New York Hospital-Queens, Astoria, New York, USA. **Inclusion/exclusion criteria** Inclusions: not applicable Exclusions: not applicable	**Sentinel Lymph Node Biopsy** Radioactive colloid and/or dye injection SLNB performed. Removal of sentinel lymph nodes Not applicable Pathology Not applicable ALND performed.	Case report **Level of evidence** IV **Follow-up** Not applicable **Loss to follow-up** Not applicable **Study period** Not applicable **Operator details** Not stated **Outcome measures** Not applicable	**Age** 61 years **Type of surgery** Lumpectomy of left breast **Stage of disease** 1 cm x 0.5 cm **Tumour histology** Adenocarcinoma **Tumour location** Left breast, location not stated. **Receptor status** Not stated **Menopausal status** Not stated **Adjuvant therapy** Not stated

Appendix J Safety and effectiveness results tables

Table J.1 SAFETY– Wound complications – Non-randomised comparative studies

	Blanchard *et al.* 2003 Level III-2		Giuliano *et al.* 2000 Level III-2		Leidenius *et al.* 2003 Level III-2		Rietman *et al.* 2003 Level III-2		Schrenk *et al.* 2000 Level III-2		Swenson *et al.* 2002 Level III-2	
Wound complications	**SLNB N=685**	**SLNB + AC N=91**	**SLNB N=67**	**SLNB + AC N=58**	**SLNB N=35**	**AC N=35**	**SLNB N=66**	**AC N=138**	**SLNB N=35**	**AC N=35**	**SLNB N=169**	**SLNB and/or AC N=78**
Complication rate			2/67 (3%)	20/58 (35%)$^{\chi}$								
Complications												
Aspiration of fluid collection					0/35 (0%)	15/35 (43%)			0/35 (0%)	0/35 (0%)		
Chronic lymphoedema				4/58 (7%)								
Haematoma in the axilla				4/58 (7%)								
Infection	20/681 (2.9%)	8/88 (91%)$^{\alpha}$									6.3%	12.7%
Inflammation of the wound							6/63 (9.5%); necessitated antibiotic treatments	20/121 (16.7%); necessitated antibiotic treatments$^{\delta}$				
Parasthesias/numbness over the intercostobrachial nerve distribution			0/67 (0%)									
Postop. bleeding requiring reoperation												
Seroma	50/681 (7.3%)	21/89 (23.6%)$^{\beta}$	1/67 (1.5%)	9/58 (16%)	0/35 (0%)	2/35 (6%)	3/60 (5%); lasting longer than 4 weeks	18/119 (15%); lasting longer than 4 weeks^{NS}	0/35 (0%)	0/35 (0%)	3.9%; requiring aspiration	23.9%; requiring aspiration
Superficial cellulitis			1/67 (1.5%)									
Wound infection				3/58 (5%)								

Abbreviations: NS, not significant; α, p=0.006; β, p<0.001; χ, p=0.001; δ, p=0.051

Table J.2 SAFETY – Wound complications – Case series

	Acosta *et al.* 2003 Level IV	**Balch *et al.* 2003 Level IV**	**Choi *et al.* 2003 Level IV**	**Classe *et al.* 2003 Level IV**
Wound complications	**SLNB N=57**	**SLNB N=32**	**SLNB N=81**	**SLNB N=200**
Complications (unspecified)	0/57 (0%)	0/32 (0%)		
Late complications (postoperative)			0/81 (0%)*	
Abscess				4/200 (2%); axillary abscess (defined as a positive bacteriological specimen within 1 month of surgery), did not require reoperation*
Seroma			At 1-week postoperative follow-up, 6/81 (7.4%) of patients were found to have a seroma and one required needle aspiration. (Postoperative drains were not used).*	
Eretheyma			1/81 (1.2%) had erethyma at the wound and received antibiotics.*	
Lymphocoele				22/200 (11.0%); axillary lymphcoele (puncture of more than 10ml of lymph), did not require reoperation*
Lymphoedema			Lymphoedema was absent in patients receiving SLNB alone.	
	Dale & Williams 1998 Level IV	**Giuliano *et al.* 1997 Level IV**	**Hansen *et al.* 2002 Level IV**	**Kapteijn *et al.* 1998 Level IV**
Wound complications	**SLNB N=21**	**SLNB N =133**	**SLNB N =238**	**SLNB N =30**
Complications (unspecified)	0/21 (0%)	0/133 (0%)		0/30 (0%)
Complication rate			3.3% (no complication required operative intervention or hospitalization)	
Seroma			4/238 (2%); required aspiration and in 1 case the temporary placement of a Penrose drain; 1/238 (0.4%) supraclavicular seroma required aspiration	
Cellulitis			1/238 (0.4%); resolved with oral antibiotics	

*It was not clear whether these patients underwent SLNB alone or SLNB followed by AC.

Table J.2 continued SAFETY– Complications arising from surgical excision of axillary sentinel lymph nodes– Case series

	Luini *et al.* 2002 Level IV	Meijer *et al.* 2002 Level IV	Miner *et al.* 1999 Level IV	Rahusen *et al.* 2003 Level IV
Wound complications	**SLNB N =115**	**SLNB N =100**	**SLNB N = 82**	**SLNB N = 67**
Immediate complications (intraoperative)	0/115 (0%)		0/82 (0%)	
Late complications (postoperative)	0/115 (0%)		0/82 (0%)	
Infection	0/115 (0%); postoperative, in the days and weeks following SLNB			0/67 (0%)
Axillary haematoma	0/115 (0%); postoperative, in the days and weeks following SLNB			
Seroma				0/67 (0%)
Lymphocoele		8/100 (8%); developed not long after procedure, all spontaneously disappeared.		
Neurologic sequela				0/67 (0%)

	Rodier *et al.* 2000 Level IV	Sabel *et al.* 2003 Level IV	Schrenk *et al.* 2001 Level IV	van Berlo *et al.* 2003 Level IV	Yong *et al.* 2003 Level IV
Wound complications	**SLNB N = 73**	**SLNB N = 25**	**SLNB N = 83**	**SLNB N = 290**	**SLNB N = 312**
Complications (unspecified)		0/25 (0%)			0/312 (0%)
Immediate complications (intraoperative)					
Late complications (postoperative)					
Infection	0/73 (0%); wound infection		1/83 (1.2%); wound infection, treated conservatively		
Axillary haematoma	0/73 (0%)			1/290 (0.3%); required reoperation	
Seroma			1/83 (1.2%); treated conservatively		
Lymphoedema	0/73 (0%); early lymphoedema				

Table J.3 SAFETY– Anaphylactic or allergic reactions to blue dye – Non-randomised comparative studies

	Swenson *et al.* (2002) Level III-2	
Anaphylactic or allergic reactions to blue dye	**SLNB N=169**	**SLNB and/or AC N=78**
Reaction to dye	15/247 (6%) experienced a reaction to isosulfan blue dye but no difference in the proportion of SLNB or SLNB and/or AC patients reporting a dye reaction)	

Table J.4 SAFETY– Anaphylactic or allergic reactions to blue dye – Case series

	Albo *et al.* 2001 Level IV						
Anaphylactic or allergic reactions to blue dye	**SLNB N=639**						
Dye type	Isosulfan blue dye (all patients had undergone radiocolloid injection 24hr prior to surgery)						
Incidence	7/639 (1.1%) (severe anaphylactic reactions)						
Cases	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Patient age (years)	75	75	50	47	65	53	53
Interval between dye injection and anaphylactic reaction (min)	20	15	15	15	30	20	30
Symptoms							
Erythema	All seven patients experienced skin reactions (generalised erythema, urticaria or both)						
Urticaria /rash /hives							
Hypotension	All seven patients experienced cardiovascular collapse (profound hypotension and tachycardia)						
Tachycardia							
Other complications	No deaths or permanent disability occurred.						
Prior surgical[1]/mediical history	Hysterectomy; Nitroglycerin patch; conjugated estrogenic hormones (Premarin)	Hysterectomy; total knee replacement; Furosemide, Metoprolol; Enalapril	Hysterectomy; lysis of adhesions; no drugs	No surgical history; Propoxyphene; Omeprazole	Hysterectomy; no drugs	No surgical history; Fluoxitine; vitamins	Breast biopsies; segmental mastectomy; laparoscopic cholecystectomy; bilateral knee replacements; Hyzaar; Venlafaxine
Known previous allergies	Penicillin, sulpha drugs (reaction; urticaria, itching)	None	Codeine, morphine (reaction; nausea, vomiting – consistent with side effects of narcotics rather than true allergy)	Codeine (reaction; nausea, vomiting – consistent with side effects of narcotics rather than true allergy)	Iodine (severe reaction; bronchospasm and hypotension)	None	None

[1] All under general anaesthesia.

	Albo *et al.* 2001 *continued*						
Premedication / anaesthesia	Sufentanil 50µg Etomidate 20mg Rocuronium 50mg; maintained using isoflurane	Sufentanil 45µg Propofol 100mg Rocuronium 50mg; maintained using isoflurane	Fentanyl 100µg Propofol 150mg Rocuronium 100mg; maintained using isoflurane	Sufentanil 25µg Propofol 120mg Rocuronium 70mg; maintained using desflurane	Sufentanil 50µg Propofol 100mg Rocuronium 50mg; maintained using isoflurane	Sufentanil 50µg Etomidate 20mg Rocuronium 100mg; maintained using isoflurane	Fentanyl 100µg Propofol 150mg Rocuronium 100mg; maintained using isoflurane
Antibiotics used	600mg Clindamycin	1g Cefazolin	1g Cefazolin	None	1g Cefazolin	600mg Ampicillin; 80mg Gentamycin	None
Interval between antibiotic administration and incision	60	40	45	N/A	60	60	N/A
Management of reaction							
Interoperative	Phenylephrine 100µg; Epinephrine 100µg; Crystalloid 3000cc; Hydrocortisone 100mg; Diphenhydramine 50mg	Crystalloid 1800cc; Epinephrine 100µg; Hydrocortisone 100mg; Diphenhydramine 50mg	Crystalloid 1600cc; Epinephrine 200µg; Hydrocortisone 100mg; Diphenhydramine 50mg	Phenylephrine 100µg; Crystalloid 1800cc; Ephedrine 5mg x3; Hydrocortisone 100mg; Diphenhydramine 50mg	Crystalloid 1500cc; Epinephrine 200µg; Diphenhydramine 50mg; Dexamethasone 10mg	Phenylephrine 200µg; Crystalloid 2000cc, Epinephrine 100µg x 2; Hydrocortisone 100mg; Diphenhydramine 50mg	Crystalloid 1600cc; Epinephrine 200µg; Diphenhydramine 50mg; Dexamethasone 10mg
Postoperative	All seven patients required admission to ICU or equivalent for postoperative monitoring.						
Occurrence of second episode of anaphylaxis	Yes, 6hr postop.	No	No	No	No	Yes, 8hr postop.	No
Management of second reaction	Epinephrine 100µg; Crystalloid 1000cc	N/A	N/A	N/A	N/A	Epinephrine 100µg; Crystalloid 1000cc	N/A
Outcome of intended surgery	Not specifically stated for individual patients, in one patient, scheduled for segmental mastectomy, reduction mammoplasty and SLNB, the anaphylactic reaction required termination of the operation after completion of the SLNB. On a subsequent readmission, she underwent bilateral reduction mammoplasty, resegmental mastectomy for margin control, and AC (malignant cells were identified in the SLNs). The procedure was performed under general anaesthesia with the same anaesthetic agents used in the previous operation. No perioperative complications ensued.						
Length of hospital stay (days)	2	1	1	1	2	3	1
	Prolonged by a mean of 1.6 days.						

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case series

	Altinyollar *et al.* 2000 Level IV	**Blessing *et al.* 2002 Level IV**	**Cox *et al.* 2000 Level IV**
Analphylactic or allergic reactions to blue dye	**SLNB N=60**	**SLNB N=600**	**SLNB N=over 1700 patients**
Dye type	Patent blue dye	Isosulphan blue dye	Isosulfan blue dye
Incidence	0/60 (0%)	1/600 (0.2%)	~1%
Interval between dye injection and anaphylaxis			
Grade of reaction			
Symptoms			
Exanthema			Manifested by an initial wheal reaction at the injection site, followed by the development of blue hives scattered about the ipsilateral axilla, neck, groin and other intertriginous areas.
Wheezing			
Hypoxia / hypoxemia / O_2 desaturation			
Hypotension			3/more than 1700 (~0.2%) cases presented with a dramatic fall in blood pressure.
Other complications			
Prior surgical/medical history			
Known previous allergies			
Premedication / anaesthesia			
Antibiotic used			
Management of reaction			
Interoperative			Generally, reaction s responded to IV diphenhydramine and have cleared rapidly. Falls in blood pressure, approximately 30min after dye injection, were treated with small doses of epinephrine, fluid rescusitation, diphenhydramine and, in one case, methylprednisolone. All resolved.
Allergic testing			
Skin prick tests / intradermal testing			

Table J.4 continued SAFETY– Anaphylactic or allergic reactions – Case series

	Ilum *et al.* 2000 Level IV	Moffat *et al.* 1999 Level IV
Anaphylactic or allergic reactions to blue dye	**SLNB N=159**	**SLNB N=70**
Dye or radiocolloid type	Patent blue V	^{99m}Tc-labelled sulphur colloid
Incidence of reaction to dye or colloid	1/159 (0.6%)	0/70 (0%); no allergic, toxic or idiosyncratic reactions
Interval between dye injection and anaphylaxis		
Grade of reaction		
Symptoms		
Exanthema	Universal, lasting 1 week, starting on day of operation	
Wheezing		
Hypoxia / hypoxemia / O_2 desaturation		
Hypotension		
Other complications		
Prior surgical/medical history	Treated with cephalosporine for an infection at the time of surgery.	
Known previous allergies	No known previous history of allergy.	
Premedication / anaesthesia		
Antibiotic used		
Management of reaction		
Interoperative		
Allergic testing		
Skin prick tests / intradermal testing	No provocation test was performed and it is unknown whether the exanthema was drug related.	

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case series

	Montgomery *et al.* 2002 Level IV
Anaphylactic or allergic reactions to blue dye	**SLNB N=2392**
Dye type	Isosulphan blue dye
Incidence	39/2392 (1.6%)
Interval between dye injection and anaphylaxis	Documented in 35 patients (35/39 (90%)) Mean 44min Median 43min, for Grade 1 mean 49min (median 46 min, range 1-205), for Grade 2 mean 28min (range 5-50min) for Grade 3 mean 35min (median 37 range 5-100). (Inherent bias in the observation that Grade 1 reactions occur later than Grade 3 reactions. Operating room staff will immediately notice the profound hypotension definitive of a Grade 3 reaction, whereas the urticaria or hives that characterize a Grade 1 reaction are often noted only on removal of the drapes at the end of the operation.)
Grade of reaction	27/39 (69%) Grade 1 reaction; urticaria, pruritis, blue hives or a generalized rash. 3/39 (8%) Grade 2 reaction; transient hypotension (systolic bp >70) not requiring pressor support 9/39 (23%) Grade 3 reaction; hypotension (systolic bp <70) requiring pressor support
Symptoms	
Exanthema	
Wheezing	Only one patient (Grade 1 reaction) had wheezing.
Hypoxia / hypoxemia / O_2 desaturation	Only 2 patients (one grade 1 and one grade 2) had hypoxia with oxygen saturation <90% as determined by pulse oximetry.
Hypotension	
Other complications	There were no deaths.
Prior surgical/medical history	
Known previous allergies	195/2392 (8%) patients reported sulfa allergies. 5/39 (13%) patients who had reported a sulfa allergy had a due reaction (therefore 2.6% (5/195) of those who reported a sulpha allergy had an allergic reaction to ISB – this incidence is not statistically significantly different from the 1.5% (34/2197) incidence of blue dye reactions in patients with no sulfa allergy)
Premedication / anaesthesia	A combination of fentanyl, propofol, midazolam, lidocaine and/or bupivacaine was used in 33/39 (85%) reactive patients. These patients did not require general anaesthesia for their definitive surgical treatment.
Antibiotic used	16/39 (41%) of reactive patients received cefazolin before surgery, compared with 978/2353 (42%) of non-reactive patients. 2/39 (5%) of reactive patients received clindamycin compared with 197/2353 (8%) of non-reactive patients. No allergic reaction were noted in patients receiving any other type of antibiotic. The incidence of allergic reactions was not significantly different between patient who received wither cefazolin or clindamycin and patients who received neither antibiotic.
Management of reaction	
Interoperative	All patients received diphenhydramine, and the more severe cases also received corticosteroids. Only the nine patients with the Grade 3 reaction were administered epinephrine. 18/35 (51%) patients had clearly documented resolution of symptoms. Mean duration 202 min (median 143 min, range 15-600min). The most severe Grade 3 reaction required 10h of pressor support (patient was alert and communicative and exhibited no respiratory compromise and at no time required intubation).
Allergic testing	No patient underwent confirmatory testing (plasma histamine, plasma tryptase, urine methyhistamine, skin prick, radioimmunoassay or enzyme-linked immunoassay for drug specific immunoglobulin E serum antibodies. Because of the temporal relationship between dye injection and reaction, the authors inferred that the probable cause was the ISB. With the exception of lidocaine, any other medication given was administered IV and earlier in the course of operation.
Skin prick tests / intradermal testing	

Table J.4 continued SAFETY– Anaphylactic or allergic reactions – Case series

	Mostafa & Carpenter 2001 Level IV	**Pijpers *et al* 1997 Level IV**	**Rodier *et al.* 2000 Level IV**	**Tsugawa *et al.* 2000 Level IV**
Complications arising from use of dye or radiocolloid	**SLNB N=80**	**SLNB N=37**	**SLNB N=73**	**SLNB N=48**
Dye type	Methylene blue		Patent blue V	Patent blue dye
Colloid type	^{99m}Tc-labelled non-colloid	^{99m}Tc-labelled colloidal albumin		99mTc-HAS
Incidence of reaction to blue dye	0/80 (0%)		0/73 (0%)	0/48 (0%)
Incidence of reaction to radiocolloid		0/37 (0%)		0/48 (0%)
Interval between dye injection and anaphylaxis				
Urticaria /rash /hives				
Management of reaction				
Interoperative				
Postoperative				

	Uğur *et al.* 2003 Level IV	**Walker *et al.* 2002 Level IV**	**Yong *et al.* 2003 Level IV**	**Yu *et al.* 2002 Level IV**
Complications arising from use of dye or radiocolloid	**SLNB N=28**	**SLNB N=122**	**SLNB N=312**	**SLNB N=218**
Dye type	Isosulfan blue dye	Patent blue V	Patent blue dye	Methylene blue dye
Colloid type	Rhenium or tin colloid		Tin colloid	
Incidence of reaction to blue dye	0/28 (0%)	1/122 (0.8%)	0/312 (0%)	0/218 (0%)
Incidence of reaction to radiocolloid	0/28 (0%)			
Interval between dye injection and anaphylaxis		Rash apparent during operation		
Urticaria /rash /hives		Generalised urticarial rash		
Management of reaction				
Interoperative		Piriton; hydrocortisone.		
Postoperative		Rash disappeared within 48hrs		

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Cimmino *et al.* 2001 Level IV		Crivellaro *et al.* 2003 Level IV
Anaphylactic or allergic reactions to blue dye			
Dye type	Isosulfan blue dye		Patent blue dye
Cases	Case 1	Case 2 and Case 3	Case 1
Interval between dye injection and anaphylaxis	~40 min	30-40 min	10 min
Symptoms			
Urticaria /rash /hives		Blue hives – entire upper trunk and upper extremities; diffuse, blue, macropapular rash evolving into multiple coloured plaques after treatment, and remained evident for 24-48 hours.	Yes; generalised urticaria
Hypotension	Yes	No decrease in blood pressure.	Yes; profound hypotension
Bradycardia	Yes	-	
Oedema		-	
Other			Dyspnea
Known previous allergies	No history of allergies.	No known allergies	No previous history of atopy of adverse reactions to general anaesthetics. Skin prick tests with a standard panel of inhalant and food allergens were negative, and total IgE were 128kU/L.
Premedication / anaesthesia	No local anaesthetic.		
Antibiotic use	Cefazolin	Cefazolin	
Management of reaction			
Interoperative	No response to ephedrine and epinephrine; reversed with diphenhydramine, famotidine and methylprednisolone.	100mg methyprednisolone; 50mg diphenhydramine.	Patient received IV epinephrine, corticosteroids, antihistamines and plasma expanders.
Postoperative			Patient recovered within 24 hours
Outcome of intended surgery			
Allergic testing			Routine tests for allergy to local anaesthetics were negative. Skin prick test and RAST (radioallergosorbent) test for latex hypersensitivity were negative.
Skin prick tests / intradermal testing			Patch and skin prick tests for the blue dye and paraphenilendyamine were negative. The intradermal test with 100µl patent blue (2.5%) was positive, with a mean wheal diameter of 12mm compared to 10mm for histamine. Intradermal tests performed as a control in 10 health volunteers was negative.
Tryptase			Serum tryptase in blood drawn 3 hours after the acute episode was 14.2ng/ml (normal value <13.5ng/ml), whereas no abnormality in complement fractions C3 and C4 were seen.

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Efron *et al.* 2002 Level IV
Anaphylactic or allergic reactions to blue dye	
Dye type	Isosulfan blue dye
Cases	Case 1
Interval between dye injection and anaphylaxis	~ 10 min
Symptoms	
Urticaria /rash /hives	Systemic red rash (not an urticarial reaction)
Hypotension	Yes
Bradycardia	
Oedema	Yes
Other	
Known previous allergies	No known drug allergies, but after the event the patient recalled having periorbital and circumoral oedema as a reaction after application of certain eye shadows and cosmetics.
Premedication / anaesthesia	
Antibiotic use	
Management of reaction	
Interoperative	10mg IV ephedrine and IV fluid resuscitation; followed by 15mg ephedrine. BP did not improve, 1mg epinephrine and 2x50mg diphenhydramine. Additional IV and intubation. Within next 5min, 1mg epinephrine and epinephrine drip stared. In next 10min, 100mg hydrocortisone, 1g methylprednisolone. Another IV and Foley catheter placed along with 2000ml fluid bolus. Epinephrine drip discontinued and phenylephrine drip. Patient responded to methylprednisolone and phenylephrine drip. Stabilised 55min after reaction began.
Postoperative	Patient moved to ICU, remained intubated due to concern of laryngeal swelling and was sedated (2mg/hr IV midazolam). Continued to receive 80mg IV methylprednisolone every 6hr for 24hr, 50mg IV ranitidine every 8hr and 50mg IV diphenhydramine every 6hr. Received IV fluid of dextrose and half normal salineat 125ml/hr as well as a single ampule of IV sodium bicarbonate. Phenylephrine drip was required for 5hr postop. to maintain bp above 100mm Hg. Phenylephrine was weaned starting 3hr postop. and discontinued over next 2hr. Fluid intake reduced to 100mg/hr and 25mg dose of furosemide given early morning postop. day 1. Electrocardiogram, echocardiogram and cardiology consult performed due to elevated cardiac enzyme and troponin level. Echocardiogram demonstrated preserved cardiac function and serial enzymes were in normal limits. Patient started on metoprolol 25mg 2x day, lisinopril 10mg 1x day, enteric coated asprin 1x day. (Elevated enzymes and troponin though to be due to patient's transitory hypoperfusion, which combined with history of hypotension, probably caused a small enzyme leak. Patient transferred to intermediate care on afternoon of postop. day 1. Repeat echocardiogram to guarantee no significant myocardial pathology. Methylprednisolone and diphenhydramine doses reduced to half. Diet advanced to clear liquids and ranitidine given orally. Transferred to floor on postop. day 2. Diphenhydramine discontinued and steroids tapered; 40mg prednisone 2x day for 48hr, 20mg 2x day for 48hr and then discontinued. At this time, patient tolerating regular diet and ambulating. Discharged on postop. day 3. Oedema resolved by subsequent follow-up.
Outcome of intended surgery	Anaesthesia was restarted and patient endotracheally intubated. Decision made to do MRM to treat the primary lesion and to remove the nidus of the ISB.Level I AC also performed.
Allergic testing	
Skin prick tests / intradermal testing	
Tryptase	

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Galatius *et al.* 2003 Level IV			
Anaphylactic or allergic reaction to blue dye				
Dye type	Patent blue dye			
Cases	Case 1	Case 2	Case 3	Case 4
Interval between dye injection and anaphylaxis	30 minutes	30 minutes	5 minutes	Not stated
Symptoms				
Urticaria /rash /hives	Yes; distinct urticaria	Yes	Yes	Patient developed urticaria but no details were given.
Hypotension	Yes; blood pressure dropped to 70/45	Yes; blood pressure dropped slightly	Yes; lowest blood pressure measured was 58/35 despite that the patient was in the Trenedenburg position and treated with volume expansion.	
Bradycardia				
Oedema		Yes; distinct swelling of the eyelids	Yes; swelling of the hands	
Other			No bronchial spasms	
Known previous allergies	No known allergies to medicine, but patient reacts to tobacco smoke by loosing her voice.	No known allergies and no use of medicine.	No known allergies except for an allergic reaction to potatoes showing as spots on the hands. Not using any form of medicine.	
Premedication / anaesthesia				
Antibiotic use				
Management of reaction				
Interoperative	Blood pressure stabilised after injection of 10mg ephedrine. The patient also received 100mg hydrocortisone and 20mg clemastin.	Patient received 10mg ephedrine, 100mg hydrocortisone and 20mg clemastin.	Initially treated with ephedrine and quickly hereafter with a bolus of norepinephrine, 100mg hydrocortisone and 20mg clemastin. Norepinephrine was given as an infusion, 1mg in 20ml saline, 2 to 5ml per hour. Volume expansion with polyhydroxyethylene and isotonic saline.	
Postoperative	Urticaria had disappeared after 5 hours.	Urticaria faded during the operation and swelling of the eyelids disappeared after a few days.	Blood pressure normalised after 35 minutes. The patient was awakened and observed until the following day, where she was well apart from swelling of the hands.	
Outcome of intended surgery	The rest of the operation went to plan.	The rest of the operation went to plan.	Operation was cancelled when the symptoms showed, and carried out one week later with identification of the sentinel node using radiocolloid only.	
Allergic testing				
Skin prick tests / intradermal testing				
Tryptase				

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Giménez *et al.* 2001 Level IV		Kuerer *et al.* (2001a) Level IV
Anaphylactic or allergic reactions to blue dye			
Dye type	Isosulfan blue due		Isosulfan blue dye
Cases	Case 1	Case 2	Case 1
Interval between dye injection and anaphylaxis	5min	5min	40min
Symptoms			
Urticaria /rash /hives	Generalised rash, mainly on extremities	Rash with weals covering entire body.	Diffuse blue urticaria
Bronchospasm	No	No	
Pallor	Facial	Yes	
Hypotension	Yes; arterial blood pressure diminished until it could not be measured with either the monitor or sphygmomanometer	Yes	Yes
Tachycardia	Yes; heart rate increased to 145bpm		
Known previous allergies /potential sensitization sources	No source of sensitization identified on retrospective review.	Patient identified exposure to different dyes and solvents when working with painted pottery, although did not recall any allergic reaction at that time.	
Premedication / anaesthesia	Sedation; 3mg IV midazolam		
Antibiotic use	2mg IV ceftriaxone		
Management of reaction			
Interoperative	Volume replacement (crystalloids, colloids), corticosteroids, antihistamines. Patient's haemodynamic condition improved after rapid bilateral lumpectomy (arterial pressure 80/40, heart rate 110bpm). Bicarbonate was given as arterial gas measurements showed metabolic acidosis. Frusemide was given to remove residues of ISB, after arterial pressure had reached normal values.	Treatment with corticosteroids and antihistamines, and lumpectomy performed. Patient recovered haemodynamic state in next few minutes and frusemide given to remove residues of ISB. Patient was extubated without further complications apart from persistence of the rash which resolved the following day.	Symptoms rapidly responded to epinephrine, diphenhydramine and corticosterioids.
Postoperative	Patient recovered without incident and was discharged 48hrs later.		
Outcome of intended surgery	Rapid bilateral lumpectomy performed to remove blue dye and tumour.	Lumpectomy performed immediately.	
Allergic testing	No reaction to latex. Thiopentone, propofol, fentanyl, suxamethonium, rocuronium, atropine, midazolam, or β-lactam antibiotics via skin prick tests.		
Skin prick tests / intradermal testing	Skin prick 1% ISB; no reaction Intradermal 1/1000, no reaction; 1/100, reaction[a]	Skin prick 1% ISB; reaction Intradermal 1/1000, reaction; 1/100, not done	

Notes: [a] Reaction: weal equal to or larger than 10mg/ml histamine for skin prick tests and 0.1mg/ml for intradermal tests. Tests were controlled in 10 healthy subjects with no reaction in all cases.

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Kuerer *et al.* 2001b Level IV	**Laurie *et al.* 2002 Level IV**	
Anaphylactic or allergic reaction to blue dye			
Dye type	Isosulfan blue dye	Isosulfan blue dye	
Cases	Case 1	Case 1	Case 2
Interval between dye injection and anaphylaxis	Not stated	~5min	40min after start of procedure
Symptoms			
Urticaria /rash /hives	Diffuse urticaria	Diffuse urticaria	No urticaria
Wheezing		Yes	No
Hypoxia / hypoxemia / O_2 desaturation		Hypoxemia (O_2 stauration 74%)	No
Hypotension	Blood pressure dropped to 65	Yes	Yes
Tachycardia			Yes
Oedema	Severe oedema, postop.		
Known previous allergies /potential sensitization sources		Macropapular rash with penicillin; local swelling with lidocaine after a dental procedure. No previous history of exposure to isosulfan blue.	Reaction to penicillin ~ 5 years previously with tongue swelling, hives and emesis. No previous history of exposure to ISB. Received propofol, lidocaine, miazolam and fentanyl with no reaction during needle localization and biopsy three weeks prior to reaction.
Premedication / anaesthesia		Propofol, midazolam, lidocaine, fentanyl	Propofol, midazolam, lidocaine, fentanyl
Antibiotic use		Cefazolin	Cefazolin
Management of reaction			
Interoperative	Diphenhydramine hydrochloride; ephedrine	3 doses of 1μg epinephrine, followed by 2x IV 10μg doses. Emergency intubated.	Treated with 4x100μg phenylephrine, but hypotension (70/40mmHg) persisted for 30 min.
Postoperative	Monitored in intensive care, extubated and discharged the next day.	Blood pressure gradually normalized and extubated 4hr later. Patient recovered without sequelae.	Transferred to ICU for observation and recovered without any sequelae.
Outcome of intended surgery	Mammoplasty abandoned due to hypotension, but segmental mastectomy performed. Axillary node dissection and bilateral reduction mammoplasty performed two weeks later with no reaction antibiotic or anaesthetic agents.	Patient underwent SLNB and partial mastectomy without the use of ISB 2 days after positive skin test and again received propofol, midazolam, lidocaine and fentanyl preop. And IV cefazolin periop. Without any adverse events noted.	Patient underwent subsequent SLNB and bilateral partial mastectomies without the use of ISB, again patient received propofol, fentanyl, midazolam , lidocaine and cefazolin without any adverse effects.
Allergic testing			
Skin prick tests / intradermal testing		Skin prick testing negative to propofol, fentanyl and lidocaine. Intradermal testing negative to propofol, fentanyl, lidocaine and ciprofloxacin. Skin prick positive with 1% ISB, intradermal test positive with 1:1000 ISB[a]	Skin prick and intradermal tests negative for cefazolin and penicillin. Skin prick positive to 1% ISB and intradermal test positive with 1:100 ISB.
Tryptase			Unfractionated serum tryptase obtained 30 min after intraoperative hypotensive event and was elevated, 37.9ng/ml (normal range, 0-11.5ng/ml)

Notes:[a] An intradermal test was positive if there was an increase in weal size of 2x2mm after 15 min. 1M (184mg/ml) histamine and saline were used as positive and negative controls, respectively. Intradermal testing was performed in nine subjects using 1% ISB in 1:1000 and 1:100 dilutions.

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Lyew *et al.* 2000 Level IV
Anaphylactic or allergic reactions to blue dye	
Dye type	Isosulfan blue dye
Cases	Case 1
Interval between dye injection and anaphylaxis	5min
Symptoms	
Erythema	No
Urticaria /rash /hives	No
Wheezing	No
Bronchospasm	
Hypoxia / hypoxemia / O_2 desaturation	Pulse oxygen saturation (99%) dropped to 94-95%
Hypotension	Blood pressure decreased from 120/60mmHg to 75/30mmHg
Bradycardia	
Tachycardia	Heart rate increased from 80 to 85bpm (not tachycardia per se)
Oedema	Marked swelling of the eyelids and lips were seen after drapes were lifted from the face.
Known previous allergies	No history of drug or food allergies, hay fever or bronchial asthma.
Premedication / anaesthesia	2mg IV midazolam. Anaesthesia induced with 100mg propofol, 20μg sufentanil and 30mg rocuronium and maintained using isoflurane in nitrous oxide and oxygen after tracheal intubation. Diphenhydramine (50mg), 1g methylprednisolone and 20mg famotidine administered. BP maintained at 85-90/45-50mmHg with subsequent doses of phenylephrine
Antibiotic use	
Management of reaction	
Interoperative	Inspired gases changed to 100% oxygen and isoflurane discontinued temporarily. One litre of lactated Ringer's solution was rapidly infused, 50mg of ephedrine administered, with no effect on blood pressure but increased the heart rate and the occurrence of ventricular extrasystoles. After 15min, BP increased to 160/90mmHg, then settled at 100-110/50mmHg with a heart rate of 100bpm and pulse oxygen saturation of 99%. Swelling of eyelids and lips were still present at the end of the procedure. Direct laryngoscopy showed that the upper airway and vocal cords, however, appeared to be normal. Airway remained clear after extubation.
Postoperative	Facial swelling had resolved 18hr after the event.
Outcome of intended surgery	AC was performed.
Allergic testing	
Skin prick tests / intradermal testing	Intradermal testing of propofol, sufentanil, midazolam and rocuronium were negative, but 0.02ml of 0.1% ISB yielded a pruritic 5mm weal with surrounding 2.5cm flare within 20min. No reaction seen in 5 healthy control subjects.
Tryptase	
Urinary methylhistamine / plasma histamine	Plasma histamine at the time of reaction was 11.2ng/ml and 18hrs after the event was 0.92ng/ml (normal ≤1.0ng/ml).
Other	At the time of reaction, C3 and C4 serum complement levels were 90mg/dl (normal 86-184mg) and 17mg/dl (normal 20-59mg/dl). Immunoglobulin E level was 38IU/ml (normal 0-160IU/ml)

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Mullan *et al.* 2001 Level IV	
Anaphylactic or allergic reaction to blue dye		
Dye type	Patent blue V	
Cases	Case 1	Case 2
Interval between dye injection and anaphylaxis	15 min	
Symptoms		
Erythema		
Urticaria /rash /hives		Widespread rash of irregular blue wheals
Wheezing		
Bronchospasm		No
Hypoxia / hypoxemia / O_2 desaturation	Desaturating to 88%	
Hypotension	Yes	No
Bradycardia	Yes	No
Tachycardia		No
Oedema		
Known previous allergies		
Premedication / anaesthesia		
Antibiotic use		
Management of reaction		
Interoperative	No response to ephedrine and atropine, adrenaline infusion started. Operation terminated.	Received IV hydrocortisone and chlorpheniramine.
Postoperative	Patient admitted to ICU and further (unspecified) treatment was administered. Patient discharged to ward after 6hr.	By 24hr rash was fading and had disappeared by 72 hours.
Outcome of intended surgery	Surgery terminated and patient was readmitted the following week for wide local excision and axillary clearance. Anaesthetic technique unchanged and uneventful.	Reconstruction successfully completed.
Allergic testing		
Skin prick tests / intradermal testing	Skin tests performed 4 days postop. where all pre- and interoperative drugs were tested. Satisfactory negative (normal saline) and positive (0.1% histamine solution) controls were obtained, and patient showed positive reactions to blue dye at 1:10 and 1:5 concentration.	Skin tests performed 11 days postop. where all pre- and interoperative drugs were tested. Satisfactory negative (normal saline) and positive (0.1% histamine solution) controls were obtained, and patient showed reaction to dye in neat concentration.
Tryptase	0hr – 46.7; 4hr – 39.0; 24hr, 13.3 (normal 2-14ng/ml)	0h – 12.6; 4hr 7.0; 24hr – 4.1 (normal 2-14ng.ml)
Urinary methylhistamine / plasma histamine	Urinary methylhistamine: 4h – 96.0 (normal 5-20 ng.ml)	Urinary methylhistamine: 4h – 47.2 (normal 5-20 ng.ml)
Other		

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Quiney *et al.* 2003 Level IV	Sadiq *et al.* 2001 Level IV	
Anaphylactic or allergic reactions to blue dye			
Dye type	Patent blue V	Isosulfan blue dye	
Cases	Case 1	Case 1	Case 2
Interval between dye injection and anaphylaxis	25-30min	~45min	25min
Symptoms			
Urticaria /rash /hives	Large, red weals	Right arm and right chest were covered with blue hives.	Widespread blue urticaria involving both breasts and entire anterior abdominal wall extending to groin.
Bronchospasm			
Hypoxia / hypoxemia / O_2 desaturation		Oxygen saturation decreased to 92% requiring increased FIO_2	Oxygen saturation decreased to 96% requiring increased FIO_2 and positive end-expiratory pressure.
Hypotension	Developed cardiovascular collapse. Profound hypotension.	Remained haemodynamically stable	Remained haemodynamically stable
Bradycardia			
Oedema			
Medical history		History of ulcerative colitis, hypertension and asthma.	Gastroesophageal reflux.
Medication at time of surgery		Mesalamine, inhaled triamcinolone acetonide, losartan/hydrochlorothiazide and multivitamins.	Omeprazole, bupropion and conjugated oestrogens/medroxyprogesterone.
Known previous allergies		No known drug allergies.	
Management of reaction			
Interoperative	Epinephrine, IV increments of 0.1mg followed by infusion, successful in reversing the hypotension and patient recovered uneventfully.	Inhaled albuterol, 50mg IV diphenhydramine and 100mg of IV hydrocortisone were given and patient's relative hypoxia completely resolved by transference to recovery unit 80min later.	Given 50mg IV diphenhydramine and 125mg IV methylprednisolone. Oxygenation improved within minutes but the blue hives persisted for nearly 5hr which made perfusion difficult to assess. Capillary refill and dermal bleeding appeared suboptimal; difficult to determine whether this was due to impaired tissue perfusion or due to the blue hives obscuring a good view of the tissue.
Postoperative		Patient was discharged the next day.	
Outcome of intended surgery			Planned reconstruction was aborted and performed 3 days later.
Allergic testing			
Skin prick tests / intradermal testing	Skin testing positive to blue dye at 1:10 and 1:5 concentration.		
Tryptase	Serum tryptase and urinary methylhistamine levels both significantly raised.		
Urinary methylhistamine			

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Salvat *et al.* 1999 Level IV
Anaphlyactic or allergic reactions to blue dye	
Dye type	Patent blue V
Cases	Case 1
Interval between dye injection and anaphylaxis	~20min
Symptoms	
Urticaria /rash /hives	Plaque of blue papular urticaria, with each papule bordered by erythema – noticed first in skin of axillary region of the arm, and when the patient was uncovered, a similar rash was found on the thorax, abdomen, insides of legs, face and eyelids. Skin retained a slight blue colour the next day and patient passed blue urine for 24 hours.
Bronchospasm	
Hypoxia / hypoxemia / O_2 desaturation	
Hypotension	Arterial systolic pressure lowered to 70mm Hg in 10 minutes.
Bradycardia	
Oedema	
Medical history	
Medication at time of surgery	Fentanyl (200μg), hypnovel (2mg), propofol (120mg), isoflurane Augmentin (2g)
Known previous allergies	No known history of allergies
Management of reaction	
Interoperative	Patient was put into the Trendelenbourg position, and given 500ml of hydroxyethylamidon, 120mg solumedrol and 10mg polaramine. Adrenaline was not needed. The patient woke immediately.
Postoperative	Patient was transferred to the intensive care unit for 24hr.
Outcome of intended surgery	
Allergic testing	
Skin prick tests / intradermal testing	
Tryptase	
Urinary methylhistamine	

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Sprung *et al.* 2003 Level IV
Anaphylactic or allergic reactions to blue dye	
Dye type	Isosulfan blue dye
Cases	Case 1
Interval between dye injection and anaphylaxis	1min
Symptoms	
Urticaria /rash /hives	A reddish macular rash was present throughout all skin areas exposed to inspection. Postoperatively, the patient's urine was blue/green and serum was green.
Bronchospasm	
Hypoxia / hypoxemia / O_2 desaturation	End tidal CO_2 acutely decreased to 12mm Hg. Oxyhemoglobin saturation decreased to 81% and remained in the low 90%s for the next 15min. Arterial blood gases on the fraction of inspired oxygen = 1.0 were: PaO_2 of 159mm (with SpO_2 of 81%), $PaCO_2$ of 61mm Hg, base deficit of -9mEq/L and a pHa value of 7.15.
Hypotension	Systolic arterial blood pressure fell from 130 to 55mm Hg, and then became undetectable with the non-invasive blood pressure monitor.
Bradycardia	ECG fell from 60bpm to 40bpm with frequent premature ventricular contractions.
Oedema	
Medical history	Graves disease treated with radioactive iodine and hormone replacement therapy.
Premedication / anaesthesia	
Known previous allergies	Reported an allergy to penicillin (hives).
Management of reaction	
Interoperative	Epinephrine (300μg subcutaneously, 30μg IV), ephedrine (85mg IV) and glycopyrrolate (0.4mg IV) were administered , and the heart rate increased to 150bpm, whereas the systolic blood pressure remained at 60mm Hg. An epinephrine drip was initiated and an arterial line was placed and systolic blood pressure remained between 60 and 70mm Hg over the next 20min despite infusion of epinephrine, dexamethasone and intravascular volume administration. Thirty minutes after initial hypotension, the patient's arterial pressure was stable at 90/70mm Hg.
Postoperative	The patient was transferred to the postanaesthesia recovery room, with epinephrine infusion, tracheal intubation and lung mechanically ventilated. Two and a half hours after the initial event, the patient was haemodynamically stable without epinephrine drip and regained full alertness. The diffuse rash gradually diminished, but forearms and finger became markedly swollen, but gradually receded over the next 24hr.
Outcome of intended surgery	Surgery was aborted.
Allergic testing	
Skin prick tests / intradermal testing	Ten days post-discharge skin testing revealed a severe positive reaction to isosulfan blue.
Tryptase	
Urinary methylhistamine	

Table J.4 continued SAFETY– Anaphylactic or allergic reactions to blue dye – Case reports

	Stefanutto *et al*. 2002 Level IV
Anaphylactic or allergic reactions to blue dye	
Dye type	Isosulfan blue dye
Cases	Case 1
Interval between dye injection and anaphylaxis	~30min
Symptoms	
Urticaria /rash /hives	No urticaria or rash
Bronchospasm	No
Hypoxia / hypoxemia / O_2 desaturation	Saturated pulse oxygen declined marginally, 99-00% to 95-96%. End tidal CO_2 concentration remained unchanged.
Hypotension	Systolic arterial blood pressure fell from 104 to 70mmHg, further decreasing to 64mmHg and then to 52mmHg.
Bradycardia	
Oedema	Orofacial oedema
Medical history	
Premedication / anaesthesia	
Known previous allergies	
Management of reaction	
Interoperative	Repeated ephedrine (10mg) and phenylephrine (200mg) boluses were administered IV. After further decline in blood pressure, anaesthesia was reduced to the minimum necessary for amnesia, 100μg IV epinephrine was given and patients blood pressure increased transiently. Resuscitation continued with IV fluids and epinephrine in repeated 100-300μg IV boluses. 5-6 L of IV fluid and 2mg epinephrine were given during the next 30 min. A right radial artery cannula was placed for continual monitoring of arterial pressure. After 30min, frequent repeated boluses of epinephrine were still required to maintain cardiovascular stability. The right internal jugular vein was cannulated, 100mg hydrocortisone and 50mg diphenhydramine were administered and a continueous infusion of 400μg/hr of epinephrine was established. Systolic blood pressure stabilised at 100-110mm Hg.
Postoperative	Patient was admitted to intensive care and required epinephrine to maintain cardiovascular stability. Orofacial oedema resolved after 12hr and epinephrine infusion was weaned and endotracheal tube removed. Discharged home after 3 days with no residual effects.
Outcome of intended surgery	Lumpectomy was performed to remove the excess isosulfan blue and the minimise possibility of a biphasic anaphylactic reaction. Concomitant planned gynaecological surgery was cancelled.
Allergic testing	
Skin prick tests / intradermal testing	
Tryptase	Serum mast cell tryptase concentration performed but results not stated.
Urinary methylhistamine	Routine blood tests, clotting and arterial blood gases obtained but results not stated.

Table J.5 SAFETY– Skin necrosis and discolouration from blue dye – Non-randomised comparative studies

	Blanchard *et al.* 2002 Level III-2		Swenson *et al.* 2002 Level III-2	
Skin necrosis and discolouration from blue dye	**SLNB N=685**	**SLNB + AC N=91**	**SLNB N=169**	**SLNB and/or AC N=78**
Dye had not faded by time of survey	712/776 (91.8%) of patients that responded to the survey had isosulfan blue dye injection. 45/712 (6.3%) reported that dye had not faded by time of survey (median 24 months, range 15-53 post injection). For 314/712 (44.1%) of patients who reported that dye had faded, the median number of months until the dye had faded was 1 month, range 0-32.			
Blue stain (on breast, chest wall or under arm)			86/247 (35%) experienced blue staining but no difference in the proportion of SLNB or SLNB and/or AC patients reporting a dye reaction)	

Table J.6 SAFETY– Skin necrosis and discolouration from blue dye – Case series

	Altinyollar *et al.* 2000 Level IV	**Borgstein *et al.* 2000 Level IV**	**Giuliano *et al.* 1997 Level IV**	**Guenther *et al.* 1997 Level IV**
Skin necrosis and discolouration from blue dye	**SLNB N=60**	**SLNB N=217 patients, 220 cases**	**SLNB N=107**	**SLNB N=145**
Dye type	Patent blue dye	Patent blue dye	Isosulfan blue dye	Isosulfan blue dye
Accumulation of blue dye in dermal lymphatics (intense)				
Complications (unspecified)			0/107 (0%)	0/145 (0%; dye related complications)
Faint blue haze		A slight skin discolouration persisted for several months in some patients.	Several patients; persisted for several months – patients were advised prior to surgery and did not report as bothersome.	
Hypersensitivity				0/145 (0%)
Infection	0/60 (0%); due to patent blue dye injection			
Stained faeces				
Stained urine			Most patients noted green urine for 12-24hrs – patients were advised prior to surgery and did not report as bothersome.	
	Imoto & Hasebe 1999 Level IV	**Kapteijn *et al.* 1998 Level IV**	**Ratanawichitrasin *et al.* 1998 Level IV**	**Yong *et al.* (2003) Level IV**
Skin necrosis or discolouration from blue dye	**SLNB N=88 cases**	**SLNB N=30**	**SLNB N=40**	**SLNB N=312**
Dye type	Indigocarmine	Patent blue dye	Isosulfan blue dye	Patent blue dye
Accumulation of blue dye in dermal lymphatics (intense)			Some patients, number not stated	
Complications (unspecified)	0/88 (0%); including tattooing			
Faint blue haze			Several patients; those who had breast conservation treatment that included external beam radiation had a faint blue skin discoloration that persisted for several months.	1/312 (3.2%) developed bluish discoloration of the skin which resolved after a few days, with no permanent side effects.
Hypersensitivity				
Infection				
Stained faeces			Most patients; noted blue dye excreted in the urine or faeces for several hours to a few days after the procedure.	
Stained urine	Most patients had green-stained urine a few hours after the dye injection.	Urine staining blue		

Table J.6 continued SAFETY– Skin necrosis and discolouration from blue dye – Case series

	Koller *et al.* 1998 Level IV	Mokbel & Mostafa 2001 Level IV	Stradling *et al.* 2002 Level IV	Zhang *et al.* 2003 Level IV
Skin necrosis or discolouration from blue dye	**SLNB N=98**	**SLNB N=35**	**SLNB N=24**	**SLNB N=95**
Dye type	Methylene blue dye or patent blue dye	Methylene blue dye	Methylene blue dye	Sulphur colloid (dye was not used)
Lesion at injection site			5/24 (21%)	
Irritation and transient redness	1/98 (1%); possibly due to hypersensitivity			
Itching and reddening of skin				1/95 (1.1%), at radiocolloid injection site, which subsided after antihistaminic administration.
Intense erythmatous			1 patient, 3cm lesion which did not require debridement or other interventions and healed after the administration of the sulfadiazine cream.	
Necrotic lesion		0/35 (0%); local skin necrosis	1 patient, 3cm lesion at the injection site and at the incision. Lesion may be a combination of the dye injection and tissue flap necrosis due to patient's heavy smoking history. Patient given gentamycin cream and completely healed without operative intervention.	
Superficial ulceration			3 patients, 4, 5 and 10cm lesions which did not require debridement or other interventions and healed after the administration of the sulfadiazine cream.	

Table J.6 continued SAFETY– Skin necrosis and discolouration from blue dye – Case report

	Wear *et al.* 2003 Level IV
Skin necrosis or discolouration from blue dye	
Dye type	Isosulfan blue dye
Staining of endotracheal tube	On postoperative extubation, the endotracheal tube was noted to be stained with approximately 3cc of concentrated isosulfan dye. The patient maintained good oxygen saturation and breath sounds. Subsequent chest radiograph ruled out a pneumothorax or pleural effusion. Patient was admitted overnight and discharged the following morning without incident.

Table J.7 SAFETY– Complications arising from excision of extra-axillary lymph nodes – Case series

	Carcoforo *et al.* 2002[a] Level IV	**De Kanter *et al.* 2000 Level IV**	**Dupont *et al.* 2001 Level IV**	**Estourgie *et al.* 2003[b] Level IV**
Complications arising from excision of extra-axillary nodes.	**Extra-axillary resection N=27**	**Extra-axillary resection N=2**	**Extra-axillary resection N=36**	**Extra-axillary resection N=150**
Internal mammary artery haemorrhage				Artery was damaged in 3/150 (2.0%). Haemostasis was secured without having to resort to a more extensive exposure.
Pleural injury	Small pleural lesion, with no consequences or particular care required.			Pleural cavity accidentally opened in 7/150 (4.7%) patients. In the first two patients, a drain was inserted into the thoracic cavity and removed the next day. In the subsequent patients, the thorax was closed while the lung was inflated.
Pneumothorax			3/36 (8%); treated with intraoperative aspiration, no patients required a chest tube and no patient required a prolonged hospital stay	No pneumothorax was observed.
Postoperative complications				No other postoperative complications were observed.
Retraction of vessel				
Serous accumulation				
Traumatic bleeding		Removal of parasternal nodes was attempted in 2/14 (14.3%); was associated with bleeding in one patient.		
	Feggi *et al.* 2001 Level IV	**Galimberti *et al.* 2002 Level IV**	**Jansen *et al.* 2000 Level IV**	**Johnson *et al.* 2000 Level IV**
Complications arising from excision of extra-axillary nodes.	**Extra-axillary resection N=73**	**Extra-axillary resection N=94**	**Extra-axillary resection N=21**	**Extra-axillary resection N=10**
Internal mammary artery haemorrhage				
Internal mammary vessel injury				0/10 (0%)
Pleural injury	A minor pleural injury occurred in 1/73 (1.4%) or 1/4 (25%) of failed excisions due to location of SN. The injury had no consequences nor required particular care)	4/94 (4%); breach of pleural cavity, sutured immediately and resolved spontaneously without need for drainage.		1/10 (10%)
Pneumothorax				1/10 (10%); secondary to violation of the pleura., easily evacuated interoperatively and patient had no postop. consequences
Postoperative complications			0/21 (0%)[a]	
Retraction of vessel				
Serous accumulation		1/94 (1%); above the breached costal space, resolved after aspiration.		

Traumatic bleeding				

Table J.7 continued SAFETY– Complications arising from excision of extra-axillary lymph nodes – Case series

	Moffat *et al.* 1999 Level IV	**Paganelli *et al.* 2002 Level IV**	**Rönka *et al.* 2002 Level IV**	**Sacchini *et al.* 2001 Level IV**	**Tanis *et al.* 2002b Level IV**	**van der Ent *et al.* 2001 Level IV**
Complications arising from excision of extra-axillary nodes.	**Extra-axillary resection N=7**	**Extra-axillary resection N=62**	**Extra-axillary resection N=30**	**Extra-axillary resection N=142**	**Extra-axillary resection N=103**	**Extra-axillary resection N=65**
Haemorrhage				0/142 (0%); no substantial haemorrhage		
Internal mammary artery haemorrhage	0/7 (0%)					
Internal mammary artery injury				1/142 (0.7%); required ligation	Occasional, numbers not stated.	
Internal mammary vein injury				1/142 (0.7%); traumatic bleeding, required ligation		
Long-term sequelae					0/103 (0%)	
Neurovascular injury	0/7 (0%)					
Pleural injury		3/ 62 (4.8%); accidentally breached, tear immediately sutured and cases resolved spontaneously and drainage was not necessary.	A minimal perforation of the parietal pleura occurred in 3/170 (1.8%) of the total cases, or 3/30 (10%) of the extra axillary cases. All recovered uneventfully without pleural drainage.	3/142 (2.1%); parietal pleura, no pneumothorax and no thoracic drainage necessary	Occasional, numbers not stated.	3/65 (4.6%); uneventful recovery after vacuum drainage
Pneumothorax	0/7 (0%)					
Postoperative complications						
Retraction of vessel				0/142 (0%)		
Traumatic bleeding						

Notes: [a] Also reported by van der Ent *et al.* 1999

Table J.8 EFFECTIVENESS – Non-randomised comparative studies (convenience sample from RCT by Veronesi *et al*. 2003)

	Veronesi *et al*. 2003 Level II			
Efficacy outcomes	**AC N=100**		**SLNB N=100**	
	6 months	24 months	6 months	24 months
Axillary pain				
No	9/100 (9.0%)	61/100 (61.0%)	84/100 (84.0%)	92/100 (92.0%)
Yes, sporadic	72/100 (72.0%)	34/100 (34.0%)	14/100 (14.0%)	7/100 (7.0%)
Yes, continuous (lasting >50% of the day)	19/100 (19.0%)	5/100 (5.0%)	2/100 (2.0%)	1/100 (1.0%)
Numbness or paraesthesias on operated side				
No	15/100 (15.0%)	32/100 (32.0%)	98/100 (98.0%)	99/100 (99.0%)
Yes	85/100 (85.0%)	68/100 (68.0%)	2/100 (2.0%)	1/100 (1.0%)
Arm mobility				
80-100%	73/100 (73.0%)	79/100 (79.0%)	100/100 (100.0%)	100/100 (100.0%)
60-79%	22/100 (22.0%)	18/100 (18.0%)	0/100 (100.0%)	0/100 (0.0%)
40-59%	5/100 (5.0%)	2/100 (2.0%)	0/100 (0.0%)	0/100 (0.0%)
20-39%	0/100 (0.0%)	1/100 (1.0%)	0/100 (0.0%)	0/100 (0.0%)
<20%	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)
Aesthetic appearance of axillary scar				
Good	91/100 (1.0%)	85/100 (85.0%)	98/100	100/100 (100.0%)
Bad	9/100 (9.0%)	15/100 (15.0%)	2/100	0/100 (0.0%)
Arm swelling (difference in circumference)				
No difference	31/100 (31.0%)	25/100 (25.0%)	89/100	93/100 (93.0%)
<1cm	44/100 (44.0%)	38/100 (38.0%)	11/100	6/100 (6.0%)
1-2cm	17/100 (17.0%)	25/100 (25.0%)	0/100 (0.0%)	1/100 (1.0%)
>2cm	8/100 (8.0%)	12/100 (12.0%)	0/100 (0.0%)	0/100 (0.0%)
Length of hospital stay				
Days	Mean 4.3		Mean 2.1	

Table J.9 EFFECTIVENESS – Perioperative outcomes - Non-randomised comparative studies

	Burak *et al.* 2002 Level III-2		Haid *et al.* 2002a Level III-3		Leidenius *et al.* 2003 Level III-2		Swenson *et al.* 2002 Level III-2	
Efficacy outcomes	**SLNB N=48**	**AC N=48**	**SLNB N=58**	**AC N=140**	**SLNB N=49**	**AC N=36**	**SLNB N=169**	**AC and/or SLNB N=78**
Length of hospital stay								
Days			7.5 {3-13}	11.9 {5-31}$^{\beta}$				
Placement of drains								
Closed suction wound drain	16%	100%	SLNB patients were not drained	Suction drainage continued for several days				
Drain (days per patient)	0.5	13.2$^{\alpha}$						
Breast drain					Almost all patients had breast drain placement for 1 day			
Axillary drain					Usually discharged 1st day postop. without drains	Usually discharged 2nd day postop. with drains *in situ*, removed on the 5th or 6th day postop.	27/169 (16%)[a]	67/78 (86%)[aχ]

Abbreviations: α, p<0.001; β, p=0.0001; χ, p<0.0001; { }, range Notes: [a] Drainage tube(s) include tubes placed both at the axillary site and at the primary site after mastectomy.

Table J.10 EFFECTIVENESS – Lymphoedema/arm swelling - Non-randomised comparative studies

	Blanchard *et al.* (2003) Level III-2		Burak *et al.* (2002) Level III-2		Golshan *et al.* (2003) Level III-2		Haid *et al.* (2002a) Level III-3		Haid *et al.* (2002b) Level III-2	
Lymphoedema/arm swelling	**SLNB N=685**	**SLNB + AC N=91**	**SLNB N=48**	**AC N=48**	**SLNB N=77**	**AC N=48**				
Lymphoedema	39/683 (5.7%)	31/91 (34.1%)$^{\alpha}$			2/77 (2.6%)	13/48 (27.1%)$^{\delta}$				
Mild/moderate	34/683 (4.9%)	23/91 (25.3%)								
Severe	4/683 (0.6%)	8/91 (8.8%)								
Arm circumference measurements (ratio of ipsilateral to contralateral arm)										
Mid-biceps			0.992 (0.039)	1.016 (0.041)$^{\beta}$						
Antecubital fossa			0.989 (0.032)	1.004 (0.032)$^{\chi}$						
Mid forearm			1.006 (0.068)	1.010 (0.062)^{NS}						
Wrist			1.004 (0.032)	1.012 (0.032)^{NS}						
Swelling										
Arm							2/57 (3.5%)	38/140 (27%)$^{\alpha}$		
Forearm							2/57 (3.5%)	29/140 (21%)$^{\varepsilon}$		
Hand							1/57 (2%)	21/140 (15%)$^{\phi}$		
Continuous							2/57 (3.5%)	17/140 (12%) ^{NS}		
Stress-related							0/57 (0%)	13/140 (9%)$^{\gamma}$		
Recurrent							1/57 (2%)	16/140 (11.5%)$^{\eta}$		
Continuous							1/57 (2%)	9/140 (6.5%) ^{NS}		
Causing a decrease in QOL							1/57 (2%)	8/140 (6%) ^{NS}		
Objective arm volume									11.95[a]	11.29$^{\iota}$
Subjective oedema									11.18[a]	9.67$^{\varphi}$

Abbreviations: NS; not significant; ( ), ± unit of error (unit not defined), [ ], ± standard deviation; α, P<0.001; β, p=0.001; χ, p=0.029; δ, relative risk =0.09 (95% confidence interval >0.02-0.39, p<0.01; ε, p0.002; ϕ, p=0.007; γ, p=0.017; η, p=0.028; ι, p=0.016; φ, p=0.002; [a] A higher scores represent less severity of symptoms.

Table J.10 continued EFFECTIVENESS – Lymphoedema/arm swelling - Non-randomised comparative studies

	Schijven *et al.* (2003) Level III-2		Rietman *et al.* (2003) Level III-2		Schrenk *et al.* (2000) Level III-2		Sener *et al.* (2001) Level III-2		Swenson *et al.* (2002) Level III-2		Temple *et al.* (2002) Level III-2	
Lymphoedema/arm swelling	**SLNB N=180**	**AC N=213**	**SLNB N=66**	**AC N=138**	**SLNB N=35**	**AC N=35**	**SLNB N=303**	**SLNB + AC N=117**	**SLNB N=169**	**SLNB and/or AC N=78**	**SLNB + AC N=117**	**AC N=28**
Lymphoedema *continued*												
Lymphoedema	2/180 (1.1%)	15/213 (7.1%)$^{\alpha}$					9/303 (3%)	20/117 (17.1%)$^{\chi}$	SLNB patients reported less arm swelling$^{\delta}$			
Interfering with daily life									AC patients more likely to report interference in daily life due to swelling$^{\varepsilon}$			
Circumference of upper arm (cm), mean change (SD)			0.9 (4.2)	0.1 (4.3)^{NS}								
Circumference of forearm (cm), mean change (SD)			0.4 (3.1)	0.0 (2.9) ^{NS}								
Arm difference (cm)												
Upper					1.14 [0.15]	1.5 [0.75]$^{\beta}$						
Forearm					0.16 [0.86]	0.95 [0.80]$^{\beta}$						
Subjective lymphoedema												
None					35	16$^{\beta}$						
Mild					0	14						
Moderate					0	5						
Severe					0	0						
Upper arm change (cm)											0.03 [1.64]	0.27 [1.25]^{NS}
Forearm change (cm)											-0.05 [0.76]	0.40 [1.10]^{NS}

Abbreviations: NS – not significant; [ ] - standard deviation; α, p<0.01, β, p=0.0001; χ, p<0.0001; δ, p=0.0005; ε, p=0.012

Table J.11 EFFECTIVENESS – Range of motion limitation - Non-randomised comparative studies

	Haid et al. 2002a Level III-3		Haid et al. 2002b Level III-2		Leidenius et al. 2003 Level III-2		Peintinger et al. 2003 Level III-2	
Range of motion limitation	**SLNB N=57**	**AC N=140**	**SLNB N=66**	**AC N=85**	**SLNB N=49**	**AC N=36**	**SLNB N=25**	**AC N=31**
Limitation of range of motion	5/57 (9%)	61/140 (43.5%)[α]						
Continuous	2/57 (3.5%)	15/140 (11%)[NS]						
Stress related	3/57 (5%)	32/140 (23%)[β]						
Recurrent	0/57 (0%)	14/140 (10%)[NS]						
Causing a decrease in quality of life	5/57 (9%)	13/140 (9%)[NS]						
Range of motion (objective)			10.55 [a]	9.18[χ]				
Abduction (objective)			11.50 [a]	11.36[NS]				
Restriction of shoulder abduction and flexion (2 weeks postop.)					24/49 (49%)	31/36 (86%)[ε]		
Subjective feelings of restricted movement (2 weeks postop.)					15/49 (31%)	5/36 (14%)		
Median deficiency in shoulder flexion					4 {0-78}	29° {0-104}[ϕ]		
Median deficiency in shoulder abduction					2° {0-118}	61° {0-118}[β]		
Axillary web syndrome					10/49 (20%)	26/36 (72%)[γ]		
Shoulder/arm mobility (after discharge)								
Abduction, mean (SD)							152.3 (13.7)	128.3 (24.9) [η]
Flexion, mean (SD)							150.6 (16.1)	134.8 (21.9) [ι]
Extension, mean (SD)							51.7 (5.0)	48.6 (11.5)
Horizontal abduction, mean (SD)							108.4 (13.2)	106.1 (15.8)
Horizontal adduction, mean (SD)							29.4 (11.3)	29.5 (14.4)
Shoulder/arm mobility (9 to 12 months after surgery)							158.9 (13.9)	143.8 (22.8) [φ]
Abduction, mean (SD)								

Flexion, mean (SD)							154.6 (15.0)	146.0 (15.9)$^{\kappa}$
Extension, mean (SD)							52.2 (21.7)	47.1 (11.2)
Horizontal abduction, mean (SD)							106.5 (21.3)	101.1 (15.9)
Horizontal adduction, mean (SD)							35.6 (19.1)	34.5 (14.1) $^{\lambda}$
Strength (subjective)			10.59 [a]	8.36$^{\alpha}$				
Strength (objective)			11.45 [a]	10.20$^{\delta}$				

Abbreviations: NS, not significant; α, p=<0.001; β, p=0.003; χ, p=0.001; δ, p=0.025; ε, p=0.002; ϕ, p<0.00001; γ, p<0.00005; η, p=0.013; ι, p=0.04; φ, p=0.007; κ, p=0.03; λ, p=0.011; [a] A higher scores represent less severity of symptoms.

Table J.11 continued EFFECTIVENESS – Range of motion limitation - Non-randomised comparative studies

	Rietman *et al.* 2003 Level III-2		Schijven *et al.* 2003 Level III-2		Schrenk *et al.* 2000 Level III-2		Swenson *et al.* 2002 Level III-2	
Range of motion limitation	**SLNB N=66**	**AC N=138**	**SLNB N=180**	**AC N=213**	**SLNB N=35**	**AC N=35**	**SLNB N=169**	**SLNB and/or AC N=78**
Forward flexion°, mean change (SD)	-10.3 (15.8)	-11.5 (23.4)^{NS}						
Abduction°, mean change (SD)	-24.7 (40.6)	-26.4 (38.4) ^{NS}						
Abduction/external rotation°, mean change (SD)	-7.2 (13.1)	-8.7 (19.2) ^{NS}						
External rotation°, mean change (SD)	-2.1 (19.3)	-0.9 (18.1) ^{NS}						
Cannot use arm to former extent			14/180 (7.7%)	45/213 (21.2%)$^{\alpha}$				
Treated by a physiotherapist			20/180 (11.2%)	80/213 (37.6%)$^{\alpha}$				
Currently being treated by a physiotherapist			19/180 (10.3%)	40/213 (18.8%)$^{\beta}$				
Loss of full arm active range of motion			11/180 (6.0%)	39/213 (18.3%)$^{\beta}$				
Use of other hand due to discomfort on affected side			8/180 (4.5%)	44/213 (20.6%)$^{\alpha}$				
Arm mobility (0-3)								
0					35/35 (100%)	29/35 (83%)$^{\chi}$		
1					0/35 (0%)	4/35 (11%)		
2					0/35 (0%)	2/35 (6%)		
3					0/35 (0%)	0/35 (0%)		
							SLNB patients had less limitation in range of motion$^{\delta}$	
							AC patients more likely to report interference in daily life due to limitation in range of motion$^{\varepsilon}$	
Arm stiffness					0/35 (0%)	2/35 (6%)^{NS}		
Grip strength (Nm), mean difference (SD)	-5.8 (94.1)	-16.9 (86.5)^{NS}						
Strength of shoulder abductors (Nm), mean difference (SD)	-15.9 (55.8)	-17.3 (51.0) ^{NS}						
Strength of elbow flexors (Nm), mean difference (SD)	-14.4 (59.2)	-15.5 (59.1) ^{NS}						
Loss of strength in arm/hand			7/180 (3.9%)	56/213 (26.3%)$^{\alpha}$				
Arm strength (0-3)								
0					35/35 (100%)	32/35 (91.5%)^{NS}		
1					0/35 (0%)	3/35 (8.5%)		
2					0/35 (0%)	0/35 (0%)		
3					0/35 (0%)	0/35 (0%)		

Abbreviations: NS, not significant; α, p<0.01; β, p=0.02; χ, p=0.011; δ, p<0.0001; ε, p=0.001

Table J.12 EFFECTIVENESS – Sensory morbidities - Non-randomised comparative studies

		Baron *et al.* 2002 Level III-2												Temple *et al.* 2002 Level III-2	
Efficacy outcomes		**SLNB N=197 AC N=96**												**SLNB N=171 AC N=62**	
		Prevalence of sensations				Severity of sensations (reported as severe or very severe)				Distress caused (reported as "quite a bit" or "very" distressing)				12 months	
		Baseline		6 months		Baseline		6 months		Baseline		6 months			
		SLNB %	AC %	SLNB %	AC %	SLNB %	AC %	SLNB %	AC %	SLNB %	AC %	SLNB %	AC %	Scores	Improvement over time
Subscale	Sensation														
Discomfort	Throbbing	41	40	23	27	5	10	1	3	4	10	2	3	SLNB better$^{\chi}$	For both SLNB and AC$^{\chi}$
	Soreness	81	88	46	45	24	32	5	7	14	25	5	10		
	Aching	58	73	31	45	13	23	5	6	11	17	5	8		
	Tenderness	88	90	55	51	24	34	8	10	14	25	8	9		
	Pain	59	75$^{\alpha}$	27	30	10	19	4	8	9	20	5	8		
	Numbness	37	78$^{\chi}$	39	81$^{\chi}$	17	40$^{\chi}$	10	31$^{\chi}$	11	21	6	17$^{\beta}$		
Mobility	Pulling	60	76	35	52$^{\beta}$	13	23	6	13	10	16	5	12	SLNB better$^{\chi}$	For both SLNB and AC$^{\chi}$
	Tightness	55	80$^{\chi}$	35	65$^{\chi}$	16	29	4	17$^{\chi}$	12	27$^{\beta}$	4	14$^{\beta}$		
	Stiffness	47	70$^{\chi}$	18	46$^{\chi}$	9	26$^{\chi}$	3	9	8	21$^{\beta}$	2	9$^{\beta}$		
	Hardness	34	35	36	44	10	12	5	12	8	6	4	12		
Paraesthesias	Pricking	43	47	30	39	8	13	3	6	6	4	3	5	SLNB better$^{\chi}$	For both SLNB and AC$^{\chi}$
	Burning	36	44	17	15	10	16	3	2	8	15	2	3		
	Tingling	35	53$^{\beta}$	34	38	5	17$^{\beta}$	2	5	3	9	2	4		
	Twinging	58	60	50	54	8	13	3	7	4	6	1	6		
Piercing	Shooting	40	45	37	39	7	13	3	5	5	8	3	5	SLNB better$^{\delta}$	For both SLNB and AC$^{\chi}$
	Penetrating	20	18	12	17	7	6	2	6	5	6	2	5		
	Nagging	24	34	12	22	5	13	1	3	5	8	2	5		
	Sharpness	34	46	27	38	9	17	4	7	6	15	4	7		
Summary score														SLNB better$^{\chi}$	For both SLNB and AC$^{\chi}$

Abbreviations: α, p=0.009; β, p<0.01; χ, p<0.001; δ, p=0.015 (not significant by authors definition, p<0.01); SLNB, sentinel lymph node biopsy; AC, axillary clearance

Table J.12 EFFECTIVENESS – Sensory morbidities - Non-randomised comparative studies

	Haid *et al.* 2002a Level III-3		Haid *et al.* 2002b Level III-2		Rietman *et al.* 2003 Level III-2		Schijven *et al.* 2003 Level III-2		Schrenk *et al.* 2000 Level III-2		Swenson *et al.* 2002 Level III-2	
Numbness/paraesthesias	**SLNB N=57**	**AC N=140**	**SLNB N=66**	**AC N=85**	**SLNB N=66**	**AC N=138**	**SLNB N=180**	**AC N=213**	**SLNB N=35**	**AC N=35**	**SLNB N=169**	**SLNB and/or AC N=78**
Numbness	0/57 (0%)	69/140 (49%)$^{\alpha}$	3.70 [a]	1.80$^{\varepsilon}$								
Causing a decrease in QOL	0/57 (0%)	9/140 (6.5%)$^{\beta}$										
Paraesthesia	4/57 (7%)	37/140 (26.5%)$^{\chi}$										
Improved since operation	4/57 (7%)	33/140 (23.5%)$^{\delta}$										
Causing a decrease in QOL	4/57 (7%)	6/140 (4%)^{NS}										
Numbness/Paraesthesia					42/66 (63.6%)	96/138 (69.6%)^{NS}						
Numbness of arm/hand							7/180 (3.9%)	52/213 (24.4%)$^{\varepsilon}$				
Tingling sensations of arm/hand							7/180 (3.9%)	31/213 (14.6%)$^{\varepsilon}$				
Numbness									0/35 (0%)	24/35 (69%)$^{\phi}$	SLNB patients reported less arm numbness$^{\gamma}$	
Interfering with daily life											AC patients more likely to report interference in daily life due to numbness$^{\alpha}$	

Abbreviations: NS, not significant; α, p<0.001; β, p=0.05; χ, p=0.002; δ, p=0.006; ε, p<0.01; ϕ, p=0.0001; γ, p<0.0001; [a] A higher scores represent less severity of symptoms.

Table J.12 continued EFFECTIVENESS – Sensory morbidities - Non-randomised comparative studies

	Blanchard *et al.* 2002a Level III-2		Haid *et al.* 2002a Level III-3		Haid *et al.* 2002b Level III-2	
Pain	**SLNB N=685**	**SLNB + AC N=91**	**SLNB N=57**	**AC N=140**	**SLNB N=66**	**AC N=85**
Pain	95/681 (14.0%)	35/91 (38.5%)$^{\alpha}$	8/57 (19%)	66/140 (47%)$^{\alpha}$	21.90[a]	18.64$^{\alpha}$
Mild	86/681 (12.6%)	30/91 (33.0%)	2/57 (3.5%)	25/140 (18%)$^{\alpha}$		
Moderate			6/57 (10.5%)	35/140 (25%)$^{\alpha}$		
Severe	6/681 (0.9%)	4/91 (4.4%)	0/57 (0%)	5/140 (4%)^{NS}		
Stress-related			8/57 (14%)	35/140 (25%)^{NS}		
Continuous			0/57 (0%)	6/140 (4%)^{NS}		
Causing a decrease in QOL			7/57 (12%)	14/140 (10%)^{NS}		

Table J.12 continued EFFECTIVENESS – Sensory morbidities - Non-randomised comparative studies

	Peintinger *et al.* 2003 Level III-2		Rietman *et al.* 2003 Level III-2		Schrenk *et al.* 2000 Level III-2		Swenson *et al.* 2002 Level III-2	
Pain	**SLNB N=25**	**AC N=31**	**SLNB N=66**	**AC N=138**	**SLNB N=35**	**AC N=35**	**SLNB N=169**	**SLNB and/or AC N=78**
Postoperative pain (EORTC QLQ-C30 scale scores) Mean (SD), after discharge	16.7 (20.4)	34.3 (29.2)†						
Sensory (NWC; McGill Pain Questionnaire)	0.88 (1.45)	2.29 (2.67)						
VAS	0.68 (1.03)	1.45 (1.36)	1.1 (2.1); mean change (SD)	1.3 (2.0); mean change (SD)^{NS}				
Pain, Mean (SD), 9 to 12 months after surgery								
Sensory (NWC; McGill Pain Questionnaire)	0.96 (2.46)	1.45 (2.29)$^{\beta}$						
VAS	0.68 (1.63)	1.13 (1.36)$^{\chi}$						
Pain (VAS 0-10)								
0					35/35 (100%)	19/35 (54%)$^{\delta}$		
1					0/35 (0%)	8/35 (23%)		
2					0/35 (0%)	5/35 (14%)		
3					0/35 (0%)	1/35 (3%)		
4					0/35 (0%)	1/35 (3%)		
5					0/35 (0%)	1/35 (3%)		
Pain							SLNB patients reported less pain$^{\varepsilon}$	
Interfering with daily life							AC patients more likely to report interference in daily life due to pain$^{\varepsilon}$	

Abbreviations: NS, not significant; α, p<0.05; β, p=0.025; χ, p=0.012; δ, p=0.0001; ε, p=0.002: †, p<0.001; [a] A higher scores represent less severity of symptoms.

Table J.13 EFFECTIVENESS – Activities of daily living - Non-randomised comparative studies

	Burak *et al.* 2002 Level III-2		Haid *et al.* 2002a Level III-3		Rietman *et al.* 2003 Level III-2		Schijven *et al.* 2003 Level III-2		Schrenk *et al.* 2000 Level III-2	
Activities of daily living	**SLNB N=48**	**AC N=48**	**SLNB N=57**	**AC N=140**	**SLNB N=66**	**AC N=138**	**SLNB N=180**	**AC N=213**	**SLNB N=35**	**AC N=35**
Days to normal activity (days)	SLNB patients returned to normal activity faster than AC patients[α]									
≤3	70.7%	70.7%								
4-7	14.6%	14.6%								
>7	14.7%	14.7%								
Overall symptoms			11/57 (9%)	69/140 (49%)[α]						
More than two symptoms			8/57 (14%)	57/140 (41%)[α]						
Activities of daily living										
Disability in household or job			7/57 (12%)	70/140 (50%)[α]						
Minor			7/57 (12%)	57/140 (41%)[α]						
Major			0/57 (0%)	13/140 (9%)[β]						
Household help needed postop.			3/57 (5.3%)	19/140 (14%)[NS]						
SDQ, mean change (SD)					14.3 (32.3)	15.7 (35.8)[NS]				
GARS, mean change (SD)					3.5 (7.2)	4.9 (7.5) [NS]				
Experience of difficulties at domestic tasks							14/180 (7.8%)	32/213 (15%)[χ]		
Affecting daily living									0/35 (0%)	4/35 (11%)[NS]

Abbreviations: NS, not significant; α, p<0.05; β, p=0.025; χ, p=0.012; δ, p=0.0001; ε, p=0.002

Table J.14 EFFECTIVENESS – Axillary recurrence – Comparative studies

Randomised controlled trials			
Study identifier	**No. patients[1]**	**Length of follow-up**	**Recurrence outcome**
Veronesi *et al.* 2003	516 patients (257 patients in the axillary dissection group and 259 in the sentinel node biopsy + axillary dissection if sentinel node positive group)	Median 46 months	The study had 84% power to distinguish between an acceptable percentage (5%) and an unacceptable percentage (10%) of women with nodal metastases at five years. A sensitivity analysis of the power of this one-sided test showed that it varied between 77 and 91% for a range of acceptable expected percentages less than 5%. The 516 patients have been followed up for a median of 46 months. At the most recent follow-up, there have been 34 events (21 in the axillary dissection group and 13 in the sentinel node group p=0.13 by the log-rank test). Of the 25 events associated with breast cancer, 15 occurred in the axillary dissection group (recurrence in the ipsilateral breast in 1, a tumour in the contralateral breast in 2, and distant metastases in 10) and 10 occurred in the sentinel node group (recurrence in the ipsilateral breast in 1, a tumour in the contralateral breast in 3, and distant metastases in 6) (p=0.26 by the log-rank test). Thus far, the rate of events associated with breast cancer is 16.4 per 1000 per year (95% CI 9.2-26.9) in the axillary dissection group and 10.1 per 1000 per year (95% CI 4.9-18.5) in the sentinel node group. Eight patients have died, 6 in the axillary dissection group (two from metastatic breast cancer) and 2 in the sentinel node group (1 from metastatic breast cancer) (p=0.15 by the log rank test). There was no statistically significant difference in the rate of overall survival between the two groups. As of the most recent follow-up, axillary recurrences have not been detected by physical or ultrasonographic examination.
Non-randomised comparative studies			
Study identifier	**No. patients[1]**	**Length of follow-up**	**Recurrence outcome**
Blanchard *et al.* 2003	894 (776 patients analysed)	Mean 2.4 ± 0.9 (SD) years	Of the node negative patients included in the study, eight died of metastatic breast cancer (6 patients had undergone SLNB only and 2 had undergone SLNB with ALND). Eight patients developed distant metastases during follow-up (3 ultimately died of the disease and 5 were alive with the disease at the time of the survey. Locally recurrent disease was seen in 6 patients: 5 had in-breast or chest wall recurrences and 1 had an axillary recurrence. The median time to local-regional recurrence was 30 months (range 4-49). The patient with axillary disease had undergone mastectomy and SLNB, with 2 negative nodes confirmed by H&E and IHC. The patient received adjuvant chemotherapy. An axillary mass was noted 41 months after initial operation and was excised, revealing a metastatically involved low axillary lymph node. Nineteen other axillary nodes removed at that time were negative for tumour. To date this represents the only clinical axillary failure after SLNB of 685 (0.15%) surveyed patients who had SLNB alone.
Giuliano *et al.* 2000	67	Median 39 months, minimum 24 months in survivors	No evidence of local or regional recurrence in patients who underwent SLNB without AC. (One patient developed a second primary breast cancer in the contralateral breast at 33 months and developed bone metastases at 50 months; one patient developed ovarian carcinoma at 22 months; One patient died at 12 months of liver failure from biopsy-proven angiosarcoma.)
Haid *et al.* 2002a	57	Not stated	No regional lymph node recurrence in either group

NOTES: 1 - Patients who had SLNB without completion AC, and is therefore not the total number of patients reported in the studies.

Table J.15 EFFECTIVENESS – Axillary recurrence – Case series

Study identifier	No. patients[1]	Length of follow-up	Recurrence outcome
Bauer *et al.* 2002	Not specifically stated	Mean 28, range 14 to 40 months	No axillary recurrences in any of the 332 patients (some patients had AC)
Badgwell *et al.* 2003	222	Median 32 , range 24 to 43 months	5/159 (3.1%) patients that were SLN negative and had no further axillary treatment, developed a recurrence (one local and four distant), with no isolated regional (axillary) recurrences. 6/63 (9.5%) patients that were SLN positive and underwent ALND, developed a recurrence (three local, one regional and two distant).
Balch *et al.* 2003	32	Median 24 months	At follow-up, 28/32 (87.5%) who received preoperative therapy (neoadjuvant chemotherapy) were alive. Two of the 28 surviving patients developed systemic recurrence and are currently receiving salvage therapy. No local or regional recurrences have been identified so far.
Borgstein *et al.* 1998	16	Mean 11 months	No axillary recurrences
Chung *et al.* 2002	207	Median 26 months	No attempt was made to include the sentinel lymph node biopsy sites within the radiation fields. 6/207 (2.9%) diagnosed with recurrent disease after median follow-up of 26 months; one regional recurrence, three systemic recurrences, two concurrent systemic and regional recurrences There were three axillary recurrences in total, described as follows; 48 year old woman, initially diagnosed with T1a breast cancer, treated with lumpectomy and sentinel lymph node biopsy, did not receive adjuvant whole breast irradiation. 31 months after initial diagnosis, patient presented with a local recurrence and underwent breast reexcision and repeat sentinel lymph node biopsy (which did not reveal any lymph node metastases) and adjuvant chemotherapy. 40 months after initial diagnosis, patient presented with axillary and systemic metastases. 45 year old woman, initially diagnosed with T1c breast cancer, developed an axillary recurrence 4 months after diagnosis and subsequently underwent an axillary node dissection, currently has no evidence of disease 27 months after axillary clearance. 51 year old woman initially diagnosed with T1c breast cancer, diagnosed with synchronous axillary and systemic recurrence 11 months after her initial diagnosis. Treated with salvage chemotherapy and died 2 months later of progressive disease. IHC was negative for all 3 patients as well as those who developed systemic recurrence only. Summary; 3 patients diagnosed with axillary recurrence after negative SLNB – resulting in a clinical false negative rate of sentinel lymph node biopsy of 1.4% (3 of 208).
Cox *et al.* 2000[2]	809 (146)	Mean 20 months (Mean 1 year)	No recurrences (No patient who was treated with SLNB has developed recurrent axillary nodal disease in a mapped SLN-negative axilla.)
Estourgie *et al.* 2003	599	21 months	One patient (primary tumour was a 1.8cm infiltrating ductal carcinoma grade II) developed an axillary recurrence at 21 months (22 months reported in abstract). Two sentinel nodes were removed and neither showed evidence of tumour, the left breast was treated with radiotherapy but no adjuvant systemic chemotherapy was given. After 21 months, the patient presented with a palpable left axillary recurrence and underwent axillary node dissection. Pathological evaluation of the axillary specimen showed massive tumour invasion and the lymph nodes were barely recognisable. Adjuvant radiotherapy to the axilla, supravlavicular and parasternal regions, chemotherapy and Tamoxifen were given and the patient was doing well with no evidence of disease three years after the first operation. On pathological review of the original sentinel nodes, additional serial sectioning of the sentinel nodes revealed, in one sentinel node, two clusters of approximately 10 tumour cells in the marginal sinus.

NOTE: 1 - Patients who had SLNB without completion AC, and is therefore not the total number of patients reported in the studies; 2 - Also reported in Bass *et al.* 1999a, Bass *et al.* 1999b, Bass *et al.* 1999c, Reintgen *et al.* 1997, Shivers *et al.* 2002.

Table J.15 continued EFFECTIVENESS – Axillary recurrence – Case series

Study identifier	No. patients[1]	Length of follow-up	Recurrence outcome
Fant *et al.* 2003	31	Mean 30, range 22 to 51 months	2/31 (6.5%) reported deaths at follow-up. One woman died as a result of intracranial haemorrhage unrelated to breast cancer 16 months after lumpectomy. She was free of disease at 12-month follow-up. The second death occurred from systemic metastases identified after eight adjuvant chemotherapy cycles and standard radiotherapy. This patient originally presented with a high-grade tumour measuring 1.3 cm (1/2 SLNs had <2 mm micrometastases). There was no clinical disease in the axilla. Preoperative abdominal computed tomography, chest x-ray and bone scan were negative for metastatic disease. She had an additional follow-up abdominal computed tomography scan 11 months after diagnosis that was also negative. She presented 13 months after diagnosis with metastatic disease to her liver, abdomen and bony structures of the spine and pelvis. The remaining 29 patients had routine examinations and mammography at 6-month intervals after lumpectomy and adjuvant therapy, and none of these patients have developed local recurrence, metastatic disease or axillary recurrence at follow-up.
Grube *et al.* 2002	Not specifically stated	43.73 months	No axillary recurrences
Guenther *et al.* 2003	46	Mean 32, range 4 to 61 months	No axillary recurrences, one patient developed systemic metastases to the liver, lung and bones 18 months later, this patient had an oestrogen and progesterone receptor negative T1c tumour, two positive sentinel nodes (micrometastases) and refused axillary clearance, but underwent chemotherapy.
Hansen *et al.* 2002	238	Median 38.9, range 6 to 69 months	No axillary recurrences detected at median follow-up of 38.9 months 98.3% patients are still alive with no evidence of disease, 1.7% (4/238 patients) developed metastatic disease, all of whom are alive. 3/238 (1.3%) patients died, all of causes unrelated to breast cancer. An ipsilateral breast recurrence developed in 4/238 patients (1.7%), a new ipsilateral breast cancer in 1 (0.4%) patients. 7/238 (3%) patients were diagnosed as having new non-breast cancers, including; lung cancer, colon cancer, hepatoma and angiosarcoma.
Henry-Tillman *et al.* 2002	Not specifically stated	Not stated	No axillary recurrences in patients who did not receive AC
Jakub *et al.* 2002	16	Mean 1.55 years	Four patients have developed distant metastatic and one patient developed a local recurrence.
Liang *et al.* 2001	144	Mean 13.5, range 1 to 26 months	No axillary or systemic relapse to date.
Meijer *et al.* 2002	100	Median 47 months (minimum 36 months)	5/100 (5%) Patient 1 had a local recurrence 20 months after breast conserving surgery, underwent a mastectomy and AC but no metastases were present. Was treated with chemotherapy and tamoxifen and is alive and well after 3 years. Patient 2 had a palpable tumour in the axilla detected at 24 month follow-up DCIS with diameter of 2.9cm was completely removed by breast conserving surgery. No tumour tissue was demonstrated upon examination of the sentinel node. On the basis of the patients age (52 years), tumour characteristics (2.9cm diameter, mitotic index 28) the patient was selected for chemotherapy. Patient treated with five courses of FEC in combination with radiotherapy (6300cGy in 30 fractions) on the breast. The recurrence in the axilla was treated by axillary dissection. Metastases were present in 5 of the 12 lymph nodes removed, in one there was tumour invasion of the capsule (palpable node). Neither mammography or extensive investigation to demonstrate secondaries could demonstrate tumour localisation elsewhere. Patient is alive and well after 3 years. Patients 3, 4 and 5 – distant metastases and were treated with 5 courses of FEC (fluorocil 500mg/m^2, epirubicine 90mg/m^2 and cyclofosfamide 500mg/m^2), 2/3 died as a consequence of visceral metastases and one patient was still alive, but not well at last follow-up.
Mirzaei *et al.* 2003	128	Not stated	To date, no tumour recurrence has been detected after surgery in any of the 128 patients.
Pelosi *et al.* 2002	154	Not stated	None of the patients with histologically negative sentinel nodes developed metastases during follow-up.
Ponzone *et al.* 2003	212	Median 15, range 3 to 35 months	None of the patients developed local-regional or distant recurrence.
Reitsamer *et al.* 2003	116	22.12 ± 6.38 months	No axillary or local recurrences were observed during the follow-up period.

NOTE: 1 - Patients who had SLNB without completion AC, and is therefore not the total number of patients reported in the studies.

Table J.15 continued EFFECTIVENESS – Axillary recurrence – Case series

Study identifier	No. patients[1]	Length of follow-up	Recurrence outcome
Roka *et al.* 2002	383	Median 19.5, range 0.4 to 56.5 months; in 372 patients	Recurrence in disease in 3/383 (0.8%) of patients (3/372 (0.8%) patients followed-up). Distant disease free survival was 99.2% Overall survival was 99.7% at the 19.5 month follow-up. 1/383 (0.3%) developed distant disease without local recurrence 2/383 (0.5%) developed axillary recurrence, described as follows: Patient 1 was treated for T1c invasive ductal carcinoma with high nuclear grading and negative oestrogen and progesterone receptor status. The SN was localized using blue dye and one SN was removed. Axillary disease and distant recurrence was diagnosed at 13 months after primary surgery and the patient was alive at the last follow-up, 19 months after the primary surgery. Patient 2 was treated for T2 invasive ductal carcinoma with high nuclear grading and negative oestrogen and progesterone receptor status. The SN was localized using blue dye and radiocolloid and two SNs were removed. Axillary recurrence was diagnosed 7 months after primary surgery. Nine months thereafter (16 months after primary surgery) patient was diagnosed to have distant disease and patient died 2 months later.
Roumen *et al.* 2001	100	Median 24 , range 16 to 40 months	99/100 (99%) of patients did not develop a local axillary recurrence. A 46 year old female patient was found to have residual axillary disease at 14 months after the initial SLNB. Clinical history included and excisional biopsy and diagnosis of invasive ductal carcinoma grade II, 8mm diameter. SLNB performed and one sentinel node removed along with reexcision of primary tumour. An additional mastectomy with primary reconstruction was performed 3 months after excisional biopsy. One year later, patient presented with axillary pain and a palpable lesion and AC showed more than 10 positive lymph nodes. Locoregional radiotherapy and hormone treatment (ovariectomy, tamoxifen) was started, but patient developed recurrent disease with pulmonary and bone metastases within two months. Patient died from brain metastases 26 months after initial diagnosis. A 44 year old female patient developed a local recurrence in the skin 9 months after the initial operation, which was a two-stage mastectomy for widespread invasive lobular carcinoma. At that time, no axillary recurrence was found. She was treated with tamoxifen, leading to a partial remission. Four months later a right colectomy was performed because of an invasive colon carcinoma ($pT_2N_0M_X$). Two months after the colectomy, there was an increase in the local mammary skin recurrence and a clinically suspected and pathologically confirmed axillary lymph node had developed. Locoregional radiotherapy was instigated.
Schrenk *et al.* 2001	83	Median 22, range 4 to 48 months	All 83/83 (100%) patients were alive with no local (axillary or breast) recurrences or systemic metastatic spread.
Simmons *et al.* 2003	112	Mean 7.9, range 0 to 26.6 months	The axillary recurrence rate was 1/112 (0.9%). This patient had a grade III 0.8cm infiltrating ductal carcinoma (T1bN0M0) in the upper outer quadrant and initially underwent total mastectomy with sentinel lymph node biopsy. The sentinel node was localised through concordant identification with methylene blue dye and technetium labelled colloid. Four other lymph nodes were also excised, that were identified by radiocolloid alone, but therefore did not meet the requirements of a sentinel node (hot and blue). On the basis of frozen section, haematoxylin and eosin and immunohistochemistry analysis, all five lymph nodes were negative for metastases. After the axillary recurrence, the patient underwent completion axillary dissection and 31 nodes were removed of which one was positive for metastases. The patient currently has no evidence of disease and no patient has experienced a distant recurrence.
Takei *et al.* 2002	354	Median 21, range 6 to 42 months	No patient developed an axillary relapse. Four patients initially recurred in distant organs (two of which have died) and one patient recurred in the conserved breasts.

NOTE: 1 - Patients who had SLNB without completion AC, and is therefore not the total number of patients reported in the studies

Table J.15 continued EFFECTIVENESS – Axillary recurrence – Case series

Study identifier	No. patients[1]	Length of follow-up	Recurrence outcome
Tanis *et al.* 2002a[2]	38 (4 patients received radiotherapy to the axilla)	Median 19, range 3 to 49 months	No regional recurrences were seen. Two patients with a sentinel node metastasis and one patient with a tumour negative sentinel node developed distant metastases after 6, 36 and 11 months, respectively.
van Berlo *et al.* 2003	290	4 years, 7 months (July 1997 to February 2002)	No local failures were documented.
Veronesi *et al.* 2001	187	2/280 (0.7%) > 4yrs; 25/280 (8.9%) 3-4yrs; 62/280 (22.1%) 2-3yrs; 191/280 (68.2%) <2yrs 343 person-years at risk at most recent follow-up	No patients have developed axillary metastases. (One patient developed a local breast recurrence, and is alive without evidence of disease or distant metastases; one patient developed distant metastases (bone) and is alive with the disease; all other patients are alive.)
Zervos *et al.* 2002	266	Mean 19 {9.2}	No axillary recurrences. Two patients had local recurrences which resulted in metastases to the axilla but the local event preceded the regional event in both cases.

Abbreviations: { } - variance (error measure not defined); NOTES: 1 - Patients who had SLNB without completion AC, and is therefore not the total number of patients reported in the studies; 2 - Also reported in Tanis *et al.* 2001 and Tanis *et al.* 2002b

Table J.15 continued EFFECTIVENESS – Axillary recurrence – Case reports

Case reports			
Study identifier	**No. patients**	**Length of follow-up**	**Recurrence outcome**
Agnese *et al.* 2003	Not applicable	Approximately 1 year (when supraclavicular mass identified)	A palpable supraclavicular mass without associated axillary adenopathy appeared approximately 1 year after lumpectomy and axillary sentinel lymph node biopsy for treatment of a T1N0M0, oestrogen receptor negative, progesterone receptor positive, Her-2/*neu* negative breast cancer. Surgical treatment was followed by adjuvant Adriamycin and cyclophosphamide, radiation therapy (5040 cGy to the breast with a 1000 cGy boost to the lumpectomy site), and tamoxifen. A CT scan of the neck revealed left supraclavicular lymphadenopathy extending into the posterior triangle of the left neck. Fine needle aspiration biopsy showed poorly differentiated metastatic adenocarcinoma consistent with the breast primary. A full staging examination showed no evidence of additional metastases. Breast MRI was negative. A left modified neck dissection was performed and 14/15 lymph nodes were involved with metastatic adenocarcinoma. Tamoxifen was discontinued and letrozole was begun. External beam radiation to the left supraclavicular region and lower neck was administered.
Cserni 2000	Not applicable (Note: patient had AC after SLNB)	15 months (when identified as a recurrence)	Axillary recurrence was treated with excision, axillary radiotherapy and anthracycline based chemotherapy. The patient was well 12 months later.
Loza *et al.*2002	Not applicable	28 months (when axillary mass identified)	First relapse in a series of 168 procedures with a median follow-up of 21 (range 48-1*** months) Complete axillary node dissection revealed metastases in 1/14 nodes. Patient was treated with chemotherapy and axillary radiotherapy.
Salmon *et al.* 2002	Not applicable	19 months (when axillary mass identified)	Complete axillary node dissection revealed 6/12 massively invaded nodes. Patient was treated with chemotherapy and axillary radiotherapy. (Patient's tumour histology was medullary carcinoma, which is not a contraindication for SLNB).
Yen *et al.* 2003	Not applicable	24 months (when axillary mass identified)	Two years after initial diagnosis, patient noticed a firm 1.0 cm mass at site of prior axillary sentinel node biopsy incision. She had no palpable cervical supraclavicular adenopathy. Her right chest wall had no evidence of recurrence. She underwent a level I, II and III axillary lymph node dissection, revealing 6 of 6 level I nodes, 25 of 25 level II nodes and 15 of 15 level III nodes positive for metastatic carcinoma, with focal extracapsular extension by tumour. Due, to extensive axillary recurrence, patient underwent aggressive concurrent Taxol chemotherapy and radiation therapy, followed by Adriamycin and Taxotere consolidation chemotherapy. Patient is disease-free 21 months after axillary recurrence.

Appendix K Randomised controlled trials in progress

There are four major trials of SLNB compared with AC that are ongoing or recently completed which are described in detail below. There are also a number of other multicentre and single centre studies focusing on various sub-questions around SLNB. All of these trials are summarised in Tables K1 and K2.

Trials in progress

NSABP B-32

The NSABP (National Surgical Adjuvant Breast and Bowel Project) B-32 trial is sponsored by the National Cancer Institute (NCI) and is being conducted through the University of Vermont, Burlington, Vermont, USA.

Objectives

- Compare the long-term control of regional disease by sentinel node resection versus sentinel node resection followed by conventional axillary dissection in women with breast cancer who are clinically and pathologically node negative.
- Compare the effect of the two regimens on the overall and disease free survival of these patients.
- Compare the morbidity associated with the two regimens in these patients.
- Determine the potentially increased risk of systemic recurrence in patients who are node negative by pathology.
- Determine the technical success rate of sentinel node dissection and the variability of technical success rate in a broad population of surgeons.
- Determine the sensitivity of the sentinel node to determine the presence of nodal metastases in these patients.
- Compare the severity of self-assessed symptoms and activity limitations of patients treated with these two regimens.
- Compare the severity of self-assessed symptoms and activity limitations after breast cancer surgery in patients whose surgery was on the dominant side versus women whose surgery was on the non-dominant side.
- Determine the impact of arm oedema, range of motion and sensory neuropathy on self assessed measures of daily functioning, symptoms and overall quality of life.

Inclusion and exclusions criteria

Females of unspecified age with life expectancy of at least 10 years (excluding diagnosis of cancer) with resectable invasive adenocarcinoma of the breast, histologically confirmed by core or open biopsy OR confirmed by fine needle aspiration cytology and positive clinical breast examination and ultrasound or mammography. Prior excisional

biopsy or lumpectomy allowed. No bilateral malignancy or mass in the contralateral breast that is supicious, unless proven non-malignant by biopsy. No diffuse tumours or multiple malignancies in different quadrants of the breast. No other prior breast malignancy except lobular carcinoma *in situ*. No prior or concurrent breast implants. The lymph nodes must be clinically negative with no positive ipsilateral axillary lymph nodes, no prior removal of ipsilateral axillary lymph nodes, no suspicious palpable nodes in the contralateral axilla, no palpable supra- or infra-clavicular lymph nodes, unless non-malignancy proven by biopsy. There must be no ulceration, erythema, infiltration of the skin or underlying chest wall, peau d'orange or skin oedema (tethering or dimpling of the skin or nipple inversion is allowed). The hormone receptor status, menopausal, performance and haematopoietic status are not specified. No prior immunotherapy, chemotherapy (including neoadjuvant chemotherapy), hormonal therapy or radiotherapy for current cancer. There must be no hepatic, renal or cardiovascular systemic disease. No prior malignancy within the past five years with the exception of effectively treated squamous or basal cell skin cancer, surgically treated carcinoma *in situ* of the cervix, surgically treated lobular carcinoma *in situ* of the ipsilateral or contralateral breast. Nor may there be concurrent psychiatric or addictive disorders.

Trial design

It was projected that 5400 patients needed to be enrolled to give approximately 4000 sentinel node negative cases and to give adequate power to show a 2% or greater survival difference between the treatment arms (Harlow & Krag 2001). As of May 2001, 159 surgeons from 59 institutions have been approved to randomise patients into the trial and current accrual has exceeded the target rate (Krag 2001).

Stratification of patients according to surgical treatment plan (ie. lumpectomy vs mastectomy), age (≤ 49 versus ≥ 50 years), clinical tumour size (≤ 2.0cm versus 2.1-4.0cm versus at least 4.1cm). Patients are then randomised to one of two surgery arms (see Figure K1).

All patients receive ^{99m}Tc-labelled sulphur colloid injected into normal breast tissue within 1cm of the primary tumour or biopsy cavity, 0.5 to 8 hours prior to surgery. Isosulfan blue dye is injected intraoperatively around the tumour or biopsy cavity after a hotspot is identified with a gamma detector.

Quality of life is assessed at baseline, every week for three weeks and then every six months for three years. Patients are followed at one and three weeks, then every six months for three years and annually thereafter.

ACOSOG-Z0011

The ASOSOG-Z0011trial is sponsored by the National Cancer Institute (NCI) and is being conducted through the American College of Surgeons Oncology Group.

Objective

- Determine whether axillary dissection improves overall survival in patients with stage I or IIA breast cancer.

- Quantify and compare surgical morbidities associated with sentinel node dissection with or without axillary dissection in patients with stage I or IIA breast cancer.

Inclusion/exclusion criteria

Females over 18 years with at least 10 years life expectancy and histologically or cytologically confirmed stage I or IIA invasive breast cancer amenable to lumpectomy with diagnosis no more than 60 days prior to sentinel node dissection. The tumour must not be attached to the skin, underlying muscle or chest wall. There should be no concurrent bilateral malignancies, no more than one malignant tumour in the same breast, no primary malignant breast tumour other than carcinoma and no more than two positive lymph nodes (ductal or lobular carcinoma allowed). No prepectoral breast implant but subpectoral implant allowed. No prior ipsilateral axillary surgery but prior breast-conserving therapy allowed if no more than 60 days prior to sentinel node dissection. If the tumour was previously excised, the biopsy cavity should be no greater than six centimetres in diameter measured by physical exam, mammography or ultrasonography. Lumpectomy margins must be free of disease and no prior mastectomy to achieve negative margins. Medial tumours with drainage to the axilla and internal mammary chain allowed. The sentinel node must have been identified and found to contain metastatic disease. There should be no matted lymph nodes or gross extranodal disease (eg. tumour involvement in three or more nodes), no inflammatory breast carcinoma and no clinically multifocal disease not amenable to lumpectomy. Oestrogen receptor status may be positive or negative. Menopausal, performance and hematopoietic status are not specified. Biologic therapy and radiotherapy are not specified. No prior chemotherapy and no oestrogen antagonist therapy for this breast cancer. No active connective tissue disorders. Hepatic and renal disease are not specified. Patients must not be considered a poor surgical risk due to any other non-malignant systemic disease. No prior malignancies within the past five years except successfully treated basal cell or squamous cell skin cancer, surgically treated carcinoma *in situ* of the cervix or lobular carcinoma *in situ* of the ipsilateral or contralateral breast. All prior malignancies must have been curatively treated and risk of recurrence must be low. Patients should not be pregnant or nursing and should have no other medical condition contraindicating axillary node dissection or postoperative breast radiotherapy.

Trial design

It was projected that approximately 1900 patients (950 per treatment arm) will be enrolled within 3.8 years. After segmental mastectomy and sentinel node dissection, patients are stratified according to age (<or=50 vs >50 years), oestrogen receptor status (positive vs negative) and tumour size (<or=1cm vs 1.1-2 cm vs >2cm). Patients are then randomised to one of two treatment arms (See Figure K2). Patients in both arms may receive adjuvant systemic therapy at the discretion of the treating physician. Patients are followed at 30 days, at 6, 12, 18, 24, 30 and 36 months and then annually thereafter.

ALMANAC

The ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) trial is currently in progress in the UK. The trial funded by the Medical Research Council and involves 15 breast care units in the UK, including university teaching hospitals and

district general hospitals. It is coordinated from the University of Wales College of Medicine (Clarke *et al.* 2001).

The trial consists of two phases. The first phase required that each surgeon achieve a successful localisation rate of 90% and a false negative rate of 5% before proceding to the randomised phase of the trial. In phase I, 400 patients had SLNB followed by AC, performed by 10 surgeons. The localisation rate was 96.6% and the false negative rate was 5%. All surgeons met the criteria, and progressed to the randomised phase, with the first results presented by Mansel *et al.* (2004) at the ASCO 2004 annual meeting.

Primary endpoints

- Axillary morbidity.
- Health economics of the sentinel lymph node biopsy procedure compared to conventional axillary clearance.
- Quality of life in patients who undergo axillary clearance compared to those that undergo sentinel lymph node biopsy.
- Axillary recurrence rates in patients who had a negative sentinel lymph node and hence did not undergo axillary clearance.

From Clarke *et al.* 2001

Trial design

It was envisaged that 15 centres would recruit 1300 patients over 12 months, for the second randomised phase. Trial duration is three years (Clarke *et al.* 2001). During the randomisation phase, patients will be randomised to one of two arms (See Figure K3). Patients receive ^{99m}Tc-labelled human colloidal albumin, 2 to 20 hours prior to surgery, in the peritumoural area. Lymphoscintigraphy of the axilla is performed at least two hours post-injection. Patent blue dye is injected intraoperatively in the peritumoral area. The morbidity associated with the treatment (ie. lymphoedema, shoulder stiffness and sensory loss) is measured using standard parameters. Arm volume is measured preoperatively and every three months postoperatively. Shoulder movements and sensory loss are also measured. Health economics are calculated using the parameters of operating room time, length of hospitalisation, duration of and morbidity arising from the use of axillary drains. Quality of life was assessed via a questionnaire (Clarke *et al.* 2001). Patients (from both phase I (audit phase) and II (randomisation phase) of the trial) will be followed up for 18 to 24 months with four three-month visits followed by six month visits (Clarke *et al.* 2001).

SNAC

The SNAC (Sentinel Node Axillary Clearance) trial, partially funded by the National Health and Medical Research Council (NHMRC) Australia, is being conducted by the Royal Australasian College of Surgeons Section of Breast Surgery in collaboration with the NHMRC Clinical Trials Centre. The aim of the SNAC trial is to determine whether sentinel lymph node biopsy (and axillary clearance if sentinel node positive) results in less morbidity than immediate axillary clearance with equivalent cancer related outcomes.

Objectives

To compare sentinel lymph node biopsy to immediate axillary clearance in terms of:

- Early axillary morbidity.
- Observer and self-rating of arm swelling, symptoms and function.
- Axillary recurrence rates.
- Other aspects of quality of life.
- Overall survival and disease-free survival (local, distant and both).
- Use of adjuvant radiation therapy, chemotherapy and hormonal therapy.
- Number of surgical episodes and total number of days in hospital.
- Use of treatments for arm swelling, symptoms and dysfunction.

Also to:

- Determine optimal measures of arm swelling, symptoms and function; and to determine what constitutes clinically important differences in these measures.
- Compare sentinel lymph node biopsy to axillary clearance in the subgroup of patients with negative sentinel lymph nodes for the above outcomes, 1 to 5.
- Compare the sentinel lymph node negative rates for patients randomised to sentinel lymph node biopsy versus axillary clearance.
- Assess the diagnostic accuracy of sentinel lymph node biopsy among those randomised to axillary clearance who have a negative sentinel lymph node biopsy, among all institutions and within each institution.

Inclusion/exclusions criteria

Female patients with histologically or cytologically confirmed invasive breast cancer with written informed consent were included. Patients with *in situ* cancer only, clinically involved nodes where axillary surgery is deemed necessary, multicentric cancers, previous axillary surgery or previous cancer in the same breast, previous surgery for the same cancer (excluding excisional biopsy), pregnancy, women 18 years old or less, allergy to isotope or dye used, inability to give informed consent, primary tumour >3cm, inaccessible for follow-up and poor understanding of English were excluded.

Trial design

Similar to the ALMANAC trial, there are two phases. The first phase (150 patients) will provide information about study procedures and outcome measures and the second, randomised phase (1000 patients) will compare the two treatments. Stratification of patients by age (<50 versus >50 years), primary tumour (palpable versus nonpalpable), lymphatic mapping technique (blue dye plus lymphoscintigraphy versus blue dye alone) and institution. Patients are then randomised to one of two arms (see Figure K4). All patients receive ^{99m}Tc-labelled antimony colloid injected, in four sites around the tumour, on the day of or the day preceding surgery. The sentinel node is identified by lymphoscintigraphy and the location marked on the skin. When nuclear medicine facilities are not available, the localisation of the sentinel node is performed using blue dye alone and patients are stratified, as described previously. Patent blue dye is injected intraoperatively, in four sites around the tumour. Sentinel node biopsy is usually performed prior to the surgery for the primary tumour. Axillary clearance is performed if no sentinel nodes are located, if sentinel nodes are positive or if the patient is randomised to the axillary clearance arm. Patients will be assessed at 1, 6 and 12 months and then

yearly for five years. Survival and disease status will be collected indefinitely. At each assessment, measurements of arm volume, sensation and shoulder movement will be taken and quality of life questionnaires will be completed. Patients presenting with symptoms or recurrence between the follow-up periods will be assessed at that visit.

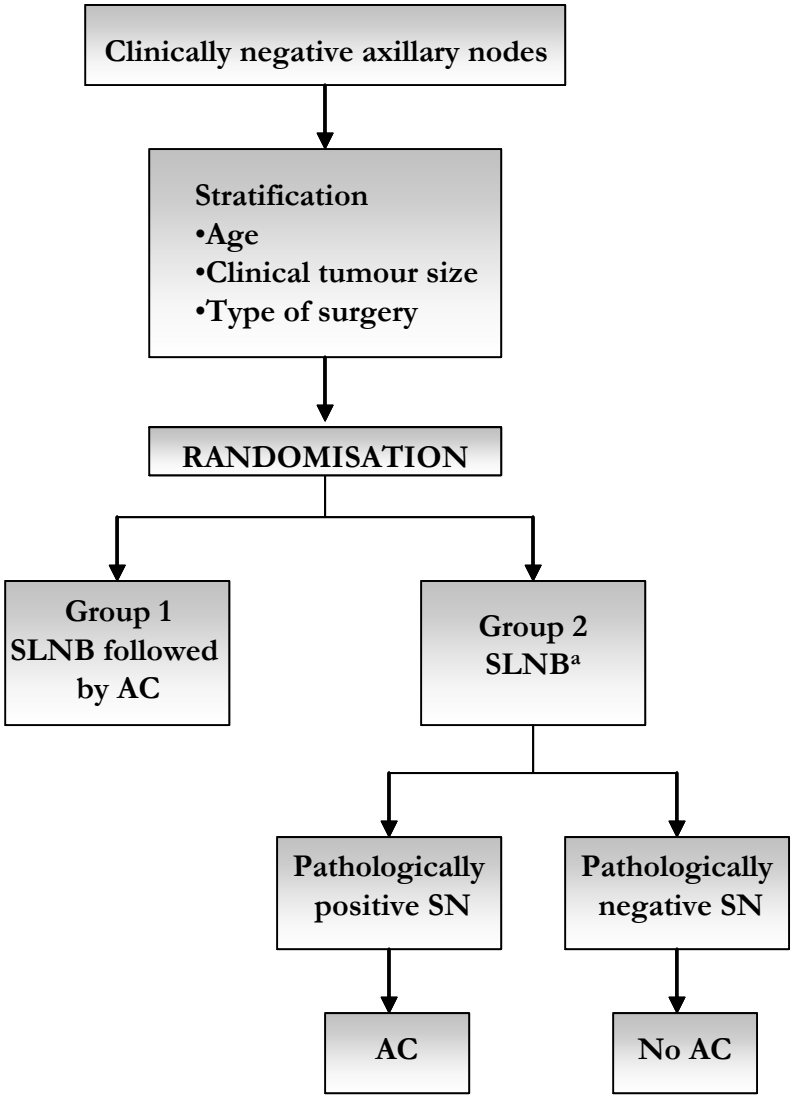

Figure K.1 Schema for the NSABP B-32

Adapted from Harlow & Krag, 2001.
[a] Patients in which a sentinel lymph node is not identified undergo axillary clearance.

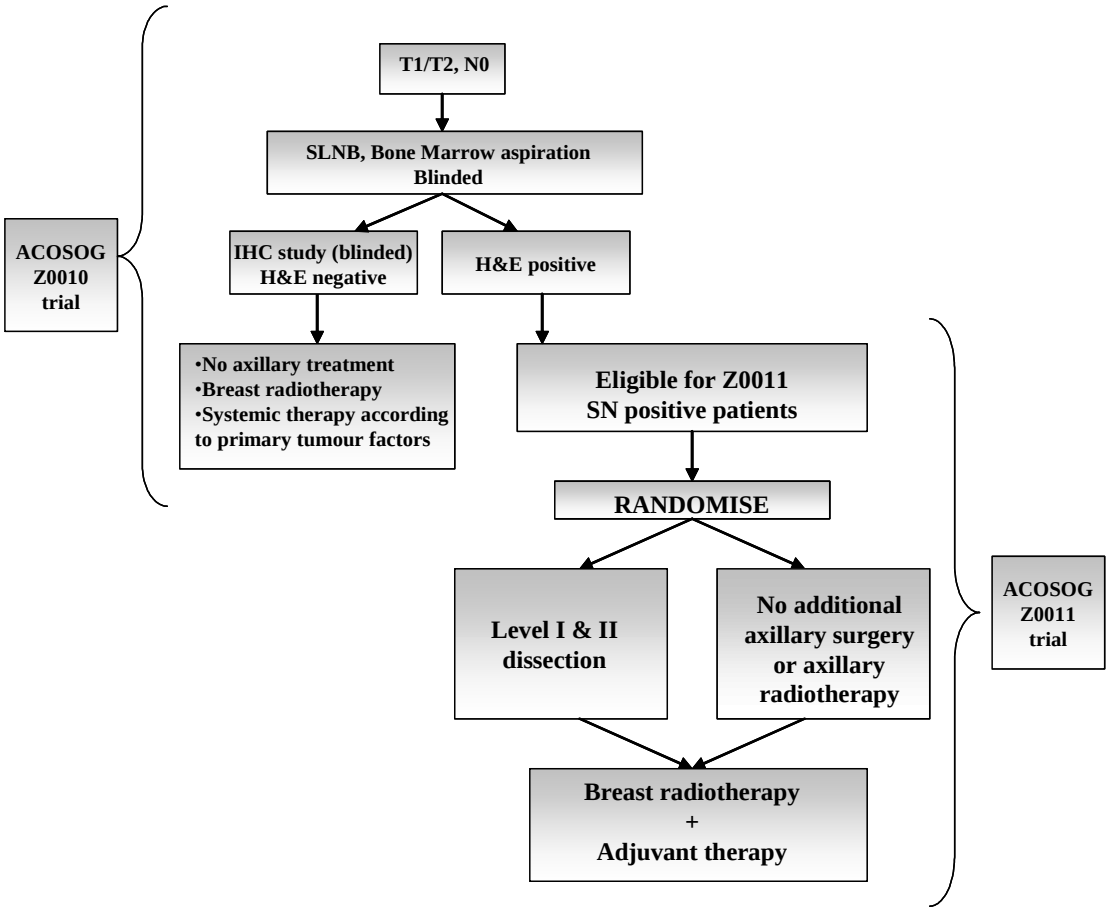

Figure K.2 Schema for the ACOSOG Z0010 and Z0011

Adapted from Ross 2001.

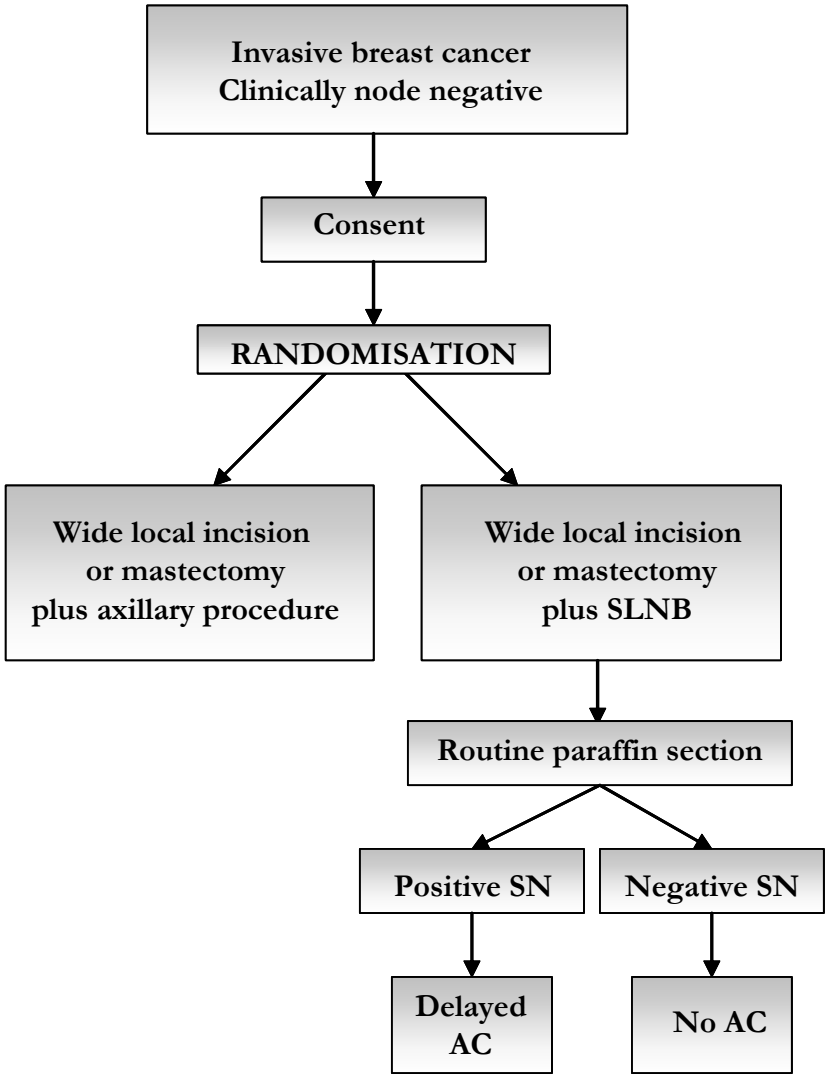

Figure K.3 Schema for the ALMANAC Phase II Protocol

Adapted from Clarke *et al.* 2001

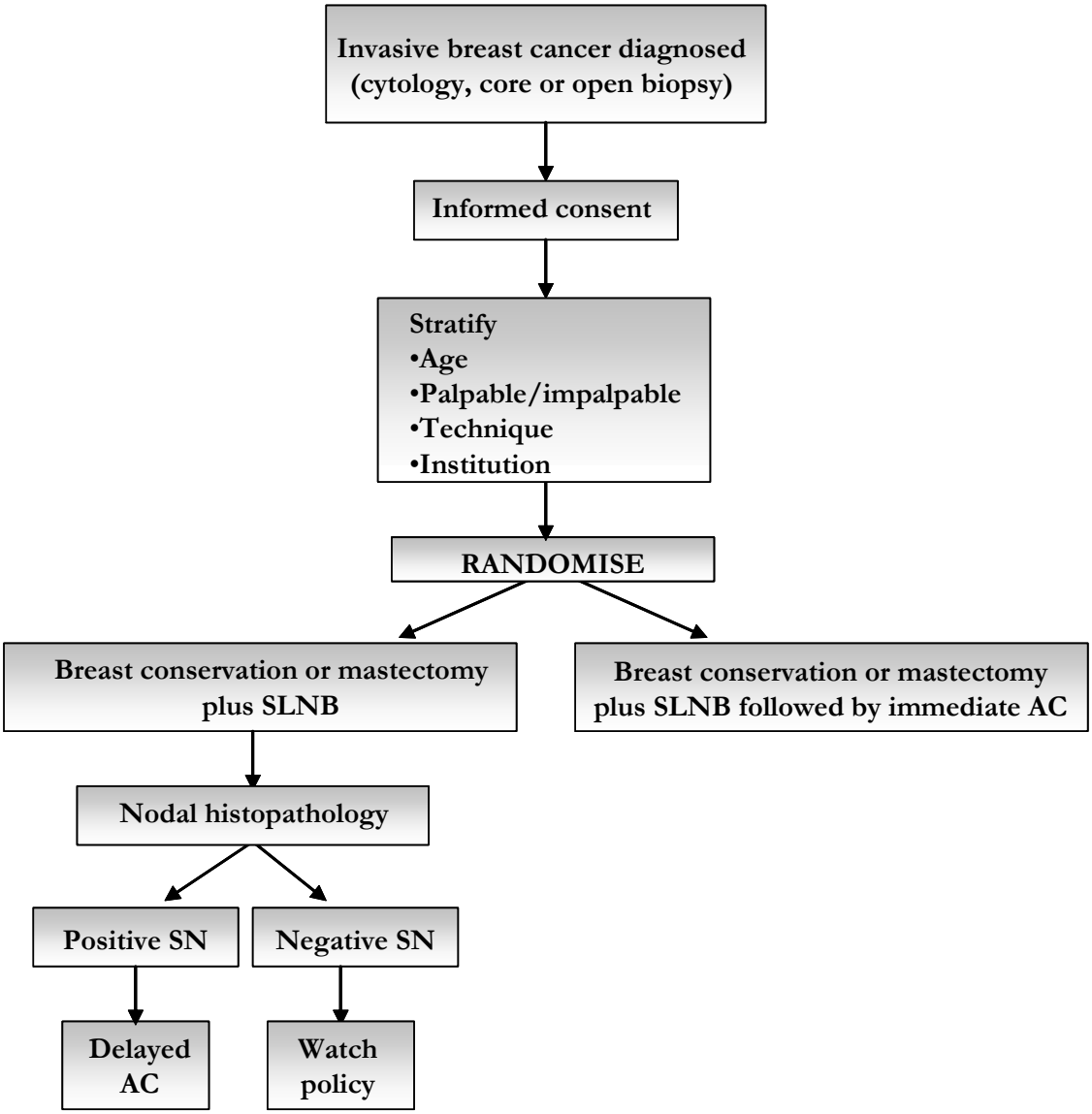

Figure J.4 Schema for the SNAC trial

Table K.1 Multicentre randomised controlled trials in progress (or completed but unpublished) at June 2004

Trial title and methodology	Accrual	Status
NSABP-B-32 *Phase III randomized study of sentinel node dissection with or without conventional axillary dissection in women with clinically node negative breast cancer.* (59 hospitals in USA and Canada) Randomisation to: • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance, • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance if node positive	5400	ongoing
ACOSOG-Z0011/GUMC-00153 *Phase III randomized study of axillary lymph node dissection in women with stage I or IIA breast cancer who have a positive sentinel node.* (USA) Randomisation to: • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance if node positive This trial will also challenge the standard practice of axillary clearance when sentinel node positive and patients with positive sentinel nodes will be randomly divided into two groups; one group will have axillary clearance and the other group will have no more lymph nodes removed.	1900	ongoing
ALMANAC *A randomised trial of sentinel node guided treatment against conventional axillary management in early breast cancer*. (15 UK Breast Units) Randomisation to • lumpectomy or mastectomy followed by axillary clearance, • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance if node positive	1300	complete
EORTC-10981 *Phase III randomised study of complete axillary lymph node dissection versus axillary radiotherapy in sentinel lymph node positive women with operable invasive breast cancer*. (22 European centres) Sentinel lymph node positive patients are randomised to: • complete axillary clearance within 8 weeks after surgery • axillary lymph node radiotherapy for 5 weeks within 8 weeks after surgery	3485	ongoing
SNAC *Sentinel lymph node biopsy versus axillary clearance in operable breast cancer.* (Australia) Randomisation to • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance, • lumpectomy or mastectomy and a sentinel node biopsy followed by axillary clearance if node positive.	1000	ongoing

Table K.2 Single centre randomised controlled trials in progress (or completed but unpublished) at June 2004)

Trial title	Accrual	Status
United Kingdom		
Sentinel node biopsy in primary breast cancer – a randomised controlled trial assessing morbidity, quality of life and cost-effectiveness.	300	ongoing
Sentinel lymph node biopsy to assess axillary lymph nodes in women with stage I or stage II breast cancer (appears to be randomised)	150	ongoing
Sentinel node biopsy for breast cancer staging	NR	ongoing
Intraoperative evaluation of sentinel lymph node using imprint cytology and immunohistochemistry staining	NR	ongoing
Randomised trial of sentinel node biopsy in breast cancer.	NR	complete
A randomised trial of sentinel node guided treatment against conventional axillary management in early breast cancer	NR	complete
United States and Europe		
Prognostic study of sentinel lymph node and bone marrow metastases in women with stage I or stage IIA breast cancer (patients who choose not to participate in ACOSOG-Z0011)	5300	ongoing
Phase III randomised study of surgical resection with or without axillary lymph node dissection in women with clinically node-negative breast cancer with sentinel node micrometastases	13000	ongoing