# Recommendations for staging and managing the axilla

## in early (operable) breast cancer

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

This document supplements the guideline recommendation on management of the *axilla* contained in the National Breast Cancer Centre* *Clinical practice guidelines for the management of early breast cancer*, 2nd edition 2001 (chapter 4.4, pages 55–59, including recommendation 9).[1]

This guideline is complemented by the NBOCC *Recommendations for use of sentinel node biopsy in early (operable) breast cancer*, 2008.[2]

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## Purpose

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

**Endorsed by:**

Breast Surgeons of Australia and New Zealand Inc.

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

The Royal Australasian College of Surgeons

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

## Background

Early (operable) breast cancer is defined as the presence of tumour/s not more than five centimetres in diameter, with *lymph nodes* (either impalpable or palpable) that are not fixed, and with no evidence of distant metastases.[1] Treatment of *early breast cancer* involves surgery to remove the tumour (a *lumpectomy* or mastectomy) and management of the *axilla* (the armpit area). The axilla is examined to assess the *stage* of the tumour (whether it has spread from the breast to surrounding *lymph* nodes – usually in the armpit), in order to determine further treatment options and prognosis.

Traditionally, the standard surgical method of axilla assessment has been removal of lymph nodes (axillary dissection) for examination by a *pathologist*. However, axillary dissection is associated with clinically significant morbidity, particularly *lymphoedema*.[2] NBOCC has published clinical practice guidelines recommending sentinel node *biopsy* (a less invasive surgical procedure) to assess the axilla in women with tumours three centimetres or less in diameter and clinically negative nodes.[2] Sentinel node biopsy may not be suitable for all women.

Following staging, further management of the axilla may be required, involving axillary dissection (if this was not part of staging) or *radiotherapy*. Staging and managing the axilla will also inform future treatment planning with the wider multidisciplinary team.

## Clinical practice recommendations

Please see statements of evidence on which the following recommendations are based.

**Recommendations to an individual should be based on their circumstances, the absolute benefits and harms of the treatment, and their personal preferences. These factors should be discussed with the woman.[3]**

| RECOMMENDATIONS | LEVEL OF EVIDENCE[4] Note: Intervention studies unless otherwise indicated | REFERENCE |
|---|---|---|
| **In women with early (operable) breast cancer:** | | |
| Management of the axilla should be determined by a multidisciplinary team in discussion with the woman | III | NBCC[1] NBCC[5] |
| The woman should be adequately prepared for the treatment or procedure. For staging and management of the axilla, this includes information on the benefits and risks of all aspects of axillary management including:<br>• sentinel node biopsy<br>• axillary dissection<br>• axillary radiotherapy<br>• observation<br>Refer to the NBOCC guidelines[1-2] for information about the clinically significant morbidity associated with axillary dissection and guidelines on sentinel node biopsy | I | NBCC & NCCI[3] |
| **AXILLARY STAGING** | | |
| Imaging alone (ultrasound, magnetic resonance spectroscopy, MRI, or PET) is not recommended for routine staging of the axilla | II/III[#] | Mobbs6 Bedrosian[7] Damera[8] Motomura[9] Sato [10] van Rijk[11] Podkrajsek[12] Mathijssen [13] Kvistad [14] Yutani[15] Barranger[16] Lovrics[17] |
| For most patients, surgical staging of the axilla is required | II | NBOCC[2] |

| RECOMMENDATIONS | LEVEL OF EVIDENCE[4] Note: Intervention studies unless otherwise indicated | REFERENCE |
|---|---|---|
| Patients with clinically or pathologically positive axillary *lymph nodes* should be recommended for axillary dissection<br><br>Patients with unifocal tumours equal to or less than three centimetres in diameter and clinically negative axillary nodes should be offered *sentinel node biopsy* as an alternative to axillary dissection<br><br>Refer to the NBOCC *Recommendations for use of sentinel node biopsy in early (operable)breast cancer*[2] for comprehensive guidelines on this procedure<br><br>Refer to statements of evidence and summary of trial or study results for information on positive sentinel node/s | II | Guiliano[18] |
| **AXILLARY TREATMENT** | | |
| For women undergoing axillary dissection, level I or II dissection is recommended as appropriate care; however, if clinically indicated a level III dissection may be performed | II | NBCC[1]<br>Tominaga[19]<br>Kodama[20] |
| For women in whom axillary dissection is contraindicated, *radiotherapy* of the axilla is recommended where the risk of axillary relapse is considered clinically significant | II | Louis-Sylvestre[21]<br>NSABP04[22] |
| In selected women with a low risk of axillary involvement, observation may be an appropriate alternative to axillary dissection | II | NSABP04 [22]<br>IBCSG [23]<br>Martelli[24] |
| Axillary radiotherapy is recommended for women at high risk of *recurrence* or suspected *residual disease* following axillary dissection | II | NBCC[1]<br>DBCG 82 b&c[25] |

[#] Studies of diagnostic accuracy were assessed using NHMRC levels of evidence specific for diagnostic studies[4]

## Statements of evidence

The following statements of evidence support the Clinical Practice Recommendations.

| STATEMENTS | LEVEL OF EVIDENCE[4] Note: Intervention studies unless otherwise indicated | REFERENCE |
|---|---|---|
| **In women with early (operable) breast cancer:** | | |
| Outcomes for women with breast cancer are better if they are treated by a clinician who has access to the full range of treatment options in a *multidisciplinary care* setting | III | NBCC[5] |
| **AXILLARY STAGING** | | |
| **SURGICAL STAGING** | | |
| **Axillary dissection**<br><br>Axillary dissection is the most accurate method for the axillary staging of breast cancer compared to axillary sampling, however it is associated with clinically significant morbidity, including lymphoedema | | NBCC[1]<br>NBOCC[2] |
| The extent of axillary *lymph* node involvement is correlated with local and systemic *recurrence* rates<br><br>The proportion of positive nodes identified is a predictor for recurrence and survival | II^<br><br>III^ | Truong[26]<br>van der Wal[27]<br>Voordeckers[28]<br>Ving-Hung[29]<br>Fortin[30]<br>Truong[31]<br>Kuru[32] |
| **Sentinel node biopsy**<br><br>Sentinel node *biopsy* is an accurate and suitable alternative to axillary dissection in women with tumours three centimetres or less in diameter to determine if cancer cells have spread to the axillary lymph nodes<br><br>Refer to the NBOCC *Recommendations for use of sentinel node biopsy in early (operable) breast cancer*, 2008 for comprehensive guidelines on this procedure[2]<br><br>*Note new evidence published since 2008**<br><br>When the sentinel node is negative, there is no significant difference in overall survival, *disease-free survival* and regional control between sentinel node biopsy followed by axillary dissection and sentinel node biopsy alone in patients with clinically negative lymph nodes | II<br><br>II | NBOCC[2]<br><br>NSABP B-32[33] |

| STATEMENTS | LEVEL OF EVIDENCE[4]<br>Note: Intervention studies unless otherwise indicated | REFERENCE |
|---|---|---|
| **Axillary sampling**<br><br>Unguided axillary sampling (followed by radiotherapy, as indicated) provides inferior axillary tumour control, compared with axillary dissection | II | Lambah[34] |
| **NON-SURGICAL STAGING (IMAGING)** | | |
| Imaging alone (without confirmatory pathology) is unreliable as a diagnostic test for axillary lymph node involvement, due to low sensitivity | II/III# | Mobbs[6]<br>Bedrosian[7]<br>Damera[8]<br>Motomura[9]<br>Sato[10]<br>van Rijk[11]<br>Podkrajsek[12]<br>Mathijssen[13]<br>Kvistad[14]<br>Yutani[15]<br>Barranger[16]<br>Lovrics[17] |
| **Ultrasound**<br><br>Ultrasound confirmed by cytology (fine needle aspiration [FNA]) or histology *core biopsy* approaches 100% specificity and 93% accuracy, but ultrasound alone has a low (≤80%) negative predictive value<br><br>A preoperative finding of ultrasound-positive nodes confirmed by FNA or core biopsy might allow the patient to proceed to axillary clearance immediately, without initial sentinel node biopsy<br><br>A negative result on ultrasound plus FNA/core biopsy would **not** remove the need for surgical axillary staging | III# | Mobbs[6]<br>Brancato[35]<br>Sapino[36]<br>Bedrosian[7]<br>Krishnamurthy[37]<br>Topal[38]<br>Damera[8] |
| **Magnetic resonance imaging (MRI)**<br><br>There are currently insufficient data available on the accuracy of MRI in axillary staging | | Murray[39]<br>Kvistad[14] |
| **Positron emission tomography (PET)**<br><br>The available data on the accuracy of PET in axillary staging vary widely between studies | II# | Greco[40]<br>Yutani[15]<br>Barranger[16]<br>Lovrics[17] |
| **AXILLARY TREATMENT** | | |

| STATEMENTS | LEVEL OF EVIDENCE[4]<br>Note: Intervention studies unless otherwise indicated | REFERENCE |
|---|---|---|
| **AXILLARY DISSECTION**<br><br>Similar clinical outcomes for survival, *local recurrence* and morbidity are achieved by either level II or III axillary dissection | II | Tominaga[19] |
| Similar clinical outcomes for survival, local recurrence and morbidity are achieved by either level I or III axillary dissection | II | Kodama[20] |
| The number of nodes retrieved at axillary dissection varies between studies, and the estimated optimal number also differs between investigators | III^ | Axelsson[41]<br>Weir[42]<br>Mersin[43]<br>Truong[31] |
| Overall, axillary recurrence rates are low following axillary dissection | II | NSABP04[22]<br>IBCSG[23]<br>Martelli[24] |
| Patients with suspected *residual disease* following axillary dissection may need further treatment | | NBCC[1] |
| **AXILLARY RADIOTHERAPY**<br><br>Radiotherapy following axillary dissection is associated with increased rates of *lymphoedema*, compared with axillary dissection alone or axillary radiotherapy alone<br><br>Five-field radiotherapy gives benefit; however the role of targeting the axilla in this technique is unclear<br><br>Radiotherapy alone to the axilla may be indicated for selected patients at high risk of microscopic disease in the axilla and with contraindications to surgery, without a survival disadvantage | III | Chang[44]<br>Grills[45]<br>Johansen[46]<br><br>Ragaz[47]<br>DBCG 82 b&c[25]<br>NSABP04[22] |

* There is no significant difference in overall or disease-free survival, or in locoregional recurrence, between women undergoing axillary lymph node dissection, or sentinel lymph node dissection alone for women eligible for the Z0011 randomised trial. These women were treated with breast-conserving surgery, whole-breast irradiation and *adjuvant systemic therapy*. Refer to Summary of trial or study results for more information on the Z0011 trial and the patient characteristics of eligible women.

^ Prognostic studies were assessed using NHMRC levels of evidence specific for prognostic studies

# Studies of diagnostic accuracy were assessed using NHMRC levels of evidence specific for diagnostic studies

## Summary of evidence

The NBOCC statements and recommendations for staging and managing the *axilla* are based on an NBOCC systematic review[48] of studies published between January 2000 and August 2007 that address the following issues in patients with early breast cancer: axillary dissection versus four-node sampling in axillary staging; axillary dissection versus non-surgical methods in axillary staging; the optimal extent of axillary dissection; the prognostic significance of the number of nodes retrieved and the number/proportion of involved nodes identified at axillary dissection; long-term outcomes of axillary dissection; and axillary *radiotherapy* (with or without axillary dissection) following breast surgery. The review included:

- four systematic reviews,[49-52] two on particular imaging techniques to *stage* the axilla and two on post-mastectomy radiotherapy
- eleven randomised controlled clinical trials[19-25, 53-58]
- approximately 90 non-randomised *clinical trials* including studies on diagnostic accuracy, prognostic studies, observational studies and case series[6-17, 26-32, 35-45, 59-121]
- one consensus statement[122] and one clinical practice guideline.[123]

Key additional studies, trials and meta-analyses relevant to this guideline were also considered after completion of the NBOCC systematic review.[18, 33, 124]

## Details of trials

**Table 1: Patient characteristics of randomised controlled trials**

| Trial, Year | Patient Numbers | Breast cancer characteristics | Patient Age / Menopausal status |
|---|---|---|---|
| Chetty, 2000[53] | 466 | Operable breast cancer, tumour size #4cm | Median age: 54yrs |
| Fisher, 2002[22] | 1665 | Primary operable breast cancer, clinically node-negative and positive | NR |
| Kodama, 2006[20] | 514 | Breast cancer (T1-3, N0, N1a, N1b) | Level I dissection vs. level III dissection<br>Mean age: 51.6yrs vs. 50.6yrs<br>Menopausal status premenopausal: 125 vs. 131 postmenopausal: 131 vs. 127 |
| Louis-Sylvestre, 2004[21] | 658 | Invasive breast cancer, tumour size <3cm, clinically node-negative | Axillary *radiotherapy* vs. axillary dissection<br>Mean age: 50.6yrs vs. 52yrs<br>Menopausal statuspremenopausal: 205pts vs.186pts,postmenopausal: 127pts vs. 140pts |
| Martelli, 2005[24] | 219 | Early breast cancer, clinically negative axillary nodes, tumour size #2cm | Age 65 to 80 years; median 70yrs |
| Morgan, 2002[54] | 76 | Operable (stage I or II) primary breast cancer, tumour *grade* III, with at least one node involved | NR |
| Overgaard 2007[25]; Nielson, 2006[56, 57] | 3083 | High-risk breast cancer patients defined as patients | Pre- and postmenopausal |

| Trial, Year | Patient Numbers | Breast cancer characteristics | Patient Age / Menopausal status |
|---|---|---|---|
| | | who were node positive and/or a T3 or T4 tumour and/or skin or deep fascia invasion | |
| Rudenstam, 2006[23] | 473 | Clinically node-negative operable breast cancer, tumour size: <2cm 56%, >2cm 42% | Age #60yrs: median 74yrs (60-91yrs) |
| Rutqvist, 2006[58] | 1226 | High-risk breast cancer patients, node-positive disease or a tumour size >30mm | Menopausal status: premenopausal 547pts<br>postmenopausal 679pts |
| Tominaga, 2003[19] | 1209 | Breast cancer *stage* II (T2 N0 or T2 N1a, excluding N1b) | Age:<40yrs: 115pts, 41-50yrs: 447 pts,<br>51-60yrs: 313pts, 61-70yrs: 253pts,<br>>71yrs: 71pts<br><br>Menopausal status:<br><br>premenopausal 567ptspostmenopausal 620pts |
| Veronesi, 2005[55] | 435 | Breast cancer with no palpable axillary nodes, tumour size #1.2cm (<0.5cm 13.1%, 0.6-1cm 61.4%, 1.1-1.2cm 16.3%, 1.2-1.5cm 9.2%) | Age >45yrs (<55yrs 40.2%, 56-65yrs 44.6%, >65yrs 15.2%) |

Note: NR = not reported

# Summary of trial or study results

## AXILLARY STAGING

### SURGICAL STAGING

#### Optimal extent of axillary dissection for staging

The findings of several non-randomised studies[41, 67, 79-80] suggest that the optimal number of nodes examined by the *pathologist* to achieve maximal accuracy was approximately 20. Conflicting findings were reported by 13 studies[27-28, 31-32, 41-43, 76, 79, 82, 89-90, 94] that investigated the association between the number of nodes excised during dissection and clinical outcomes, including survival and axillary *recurrence*.

#### Sentinel node biopsy

Sentinel node *biopsy* is an accurate and suitable alternative to axillary dissection and is recommended for women with unifocal breast cancer tumours that are three centimetres or less in diameter and with clinically negative nodes. The significance of micrometastases in the sentinel node is yet to be established. For comprehensive guidelines on sentinel node biopsy, please refer to the NBOCC *Recommendations for use of sentinel node biopsy in early (operable) breast cancer*, 2008.[2] Relevant recommendations from this guideline include:

If the sentinel node is identified at the time of sentinel node biopsy:

- For a positive sentinel node – axillary dissection is recommended (with due consideration of the risks and benefits to the individual woman)
- For a negative sentinel node – clinical follow-up of the axilla is recommended.

If the sentinel node is not identified at the time of sentinel node biopsy:

- axillary dissection should be performed.

***New evidence published since 2008***
*Positive sentinel nodes*

A recent randomised trial of 891 patients (with 446 patients randomised to no further surgery after a positive sentinel node was detected) reported results in 2011.[18*] Results indicate that for a select group of women (those with clinical T1-T2 *invasive breast cancer*, no palpable lymphadenopathy and 1 to 2 positive sentinel *lymph nodes*, who are treated with breast-conserving surgery, whole-breast irradiation and *adjuvant* systemic therapy) 5-year overall survival was not significantly different between groups randomised to axillary *lymph* node dissection (ALND) or to sentinel lymph node dissection (SLND) alone.[18] It should be noted that accrual to this trial closed earlier than anticipated due to lower than expected accrual and event rates. Due to the select group of women enrolled in the trial, the applicability of these results should be considered.

There were no significant differences between the groups in 5-year *disease-free survival*, in 5-year rate of *local recurrence* or in locoregional *recurrence-free survival* at 5 years. Surgical morbidities were higher for the group undergoing ALND than for the SLND-alone group (rate of wound infections, axillary *seromas* and paresthesias; $p<0.001$), and *lymphoedema* was significantly more common in the ALND group by subjective report ($p<0.001$). It should be noted that this study refers only to women who had *lumpectomy* and whole-breast irradiation.[18]

*Positive non-sentinel nodes*

In the Z0011 trial, 27.3% of women in the ALND group had additional *metastasis* in non-sentinel lymph nodes removed by ALND, including 10% of women with sentinel node micrometastasis who had macroscopically involved non-sentinel nodes.[18]

A meta-analysis of 56 studies to June 2009, where patients had positive sentinel node/s and underwent ALND, reported the proportion of patients with positive non-sentinel nodes ranged from 24 to 65.7% (median 38%).[124*] The meta-analysis identified eight clinicopathological variables most predictive of non-sentinel node metastases when the sentinel node is positive: SLN metastases >2mm in size, extracapsular extension in the SLN, >1 positive SLN, ≤1 negative SLN, tumour size >2cm, ratio of positive sentinel nodes >50% and lymphovascular invasion in the primary tumour and method of detection.[124]

*Negative sentinel nodes*

Further results of a randomised controlled trial confirm that in patients with negative sentinel nodes, sentinel node biopsy alone with no further axillary dissection, is an appropriate, safe and effective therapy for patients with clinically negative lymph nodes.[33*] Sentinel node biopsy was found to be statistically equivalent to axillary dissection for overall survival, disease-free survival and regional control in node-negative patients.

### Axillary sampling

Pooled 15-year follow-up data[34] showed that four-node sampling (a staging procedure comprising excision and biopsy of four lymph nodes) was associated with a significantly higher rate of axillary recurrence than axillary dissection in the subgroup of patients assessed as node-negative. However, randomised clinical trial outcome data for four-node sampling are only available from a single centre, and therefore must be interpreted with caution. Two non-randomised trials[72,88] using axillary dissection as the reference standard reported that four-node sampling was an accurate method for staging breast cancer.

## NON-SURGICAL STAGING (IMAGING)

There is insufficient evidence for the accuracy of imaging modalities (ultrasound, magnetic resonance spectroscopy, MRI or PET) in axillary staging in the absence of confirmatory pathology. Imaging alone remains unreliable as a diagnostic test for axillary lymph node involvement in *early breast cancer* due to its low sensitivity.

### Ultrasound

The overall accuracy of ultrasound alone ranged from 70% to 82% in studies using axillary dissection and/or sentinel node biopsy as the reference standard.[6, 9-10, 13, 36, 97, 99, 101] Accuracy approached 93% where ultrasound was performed in combination with either cytology *fine needle aspiration* or histology *core biopsy*.[9, 36-38, 78, 96-97] These results suggest that preoperative ultrasound Ã#± FNA/core biopsy may be useful in staging the clinically negative axilla. A preoperative finding of ultrasound-positive nodes confirmed by FNA or core biopsy might allow the patient to proceed to axillary clearance immediately, without initial sentinel node biopsy. However due to the low negative predictive value of ultrasound, a negative result on ultrasound plus FNA/core biopsy would not remove the need for surgical axillary staging.

### Magnetic resonance imaging (MRI)

The utility of MRI is limited by technical difficulties and lack of standardised criteria for a positive lymph node.[14, 39] Two small studies[14, 39] in which patients underwent dynamic contrast-enhanced MRI prior to planned level I/

II axillary dissection, reported positive predictive values of 38–83% and negative predictive values of 90–100%. Available data suggest that a positive finding on axillary MRI must be carefully interpreted and requires surgical confirmation.

### Positron emission tomography (PET)

Reported results on the accuracy of PET must be interpreted with caution, due to wide variability and the small size of several studies.[15-16, 103-106, 108] With findings on axillary dissection as the reference standard, the overall negative predictive value was low. Reported specificity was generally relatively high (80–100%), with the largest series[107,110-111] (n > 230 for each) reporting specificity values of 80–98.5% and positive predictive values of 62–98.4%. Therefore, axillary lymph node dissection may be more appropriate than a confirmatory sentinel node biopsy for axillary staging in patients with PET-positive axillary nodes to minimise the number of procedures for the woman. *Sentinel node biopsy* may still be considered, however, to avoid unnecessary axillary dissection due to the possibility of false positives. The results of one small study suggest that a combination of PET and ultrasound may increase sensitivity and accuracy compared to either modality alone, however the difference was not statistically significant.[101]

* This paper was published after NBOCC systematic review was completed

## TREATMENT

### DISEASE-FREE SURVIVAL

### Axillary dissection

Overall axillary *recurrence* rates are low following axillary dissection.[1]

Available evidence suggests there is no difference between level I/II axillary dissection and level III axillary dissection with respect to *local recurrence*. Two large randomised controlled clinical trials[19-20] with median follow-up intervals of more than seven years reported no statistically significant difference in *disease-free survival*, axillary recurrence or local recurrence between patients who underwent level I dissection compared with level III dissection[20] and between patients who underwent level II dissection compared with level III dissection.[19]

It may, however, be appropriate to perform a level III axillary clearance in certain clinical situations, in particular when obviously involved nodes are present in level III of the axilla.

The subgroup of patients at high risk of axillary recurrence following axillary dissection is not well defined due to limited data. Among older patients with clinically node-negative disease, at low risk of recurrence, two small randomised controlled clinical trials[23-24] comparing axillary dissection with observation reported no difference in rates of overall survival or local control. In the single study with the longest follow-up (NSABP04),[22] axillary dissection was not associated with a survival benefit, compared with *mastectomy* alone followed by observation or radiotherapy in clinically node-negative patients. However, local recurrence rates were high in this study population.[22]

### Axillary radiotherapy

A randomised controlled clinical trial[55] comparing breast-conserving surgery plus radiotherapy with two opposed fields (antero-posterior and postero-anterior) with surgery alone in clinically node-negative women aged over 45 years reported no significant difference in axillary recurrence rates between groups. However, the axillary recurrence rate was very low in both treatment arms.

### Axillary radiotherapy versus axillary dissection

At 25-year follow-up of the NSABP04 trial,[22] postmastectomy regional radiotherapy delivered to the internal mammary nodes, the supraclavicular nodes and the chest wall was not associated with an overall improvement in local or systemic control, either in the clinically node-negative group (compared with total mastectomy and axillary dissection or radical mastectomy alone) or in the clinically node-positive group (compared with radical mastectomy). However, among the group with negative nodes at baseline, the cumulative incidence of local or regional recurrence was lowest (1% and 4% respectively) in the group who received total mastectomy and radiotherapy.[22] The incidence of regional axillary recurrence was 4% for women who had radical mastectomy and axillary dissection; however this increased to 6% if surgery was delayed until recurrence.[22] Interpretation of early results from randomised trials requires caution as after 25-year follow-up, 25% of all first distant recurrences and 50% of all *contralateral breast* cancers were detected after 5 years.[22]

Pooled 15-year follow-up data from two randomised controlled clinical trials[34] reported that, for node-positive patients, axillary radiotherapy was associated with a non-significant trend towards reduced axillary recurrence, compared with axillary dissection alone. Fifteen-year follow-up data from a randomised trial in women with clinically uninvolved lymph nodes[21] that compared axillary radiotherapy to axillary and internal mammary lymph nodes (n=332) with axillary dissection (n=326) reported no significant difference in disease-free survival between treatment groups. No improvement in axillary recurrence rates were reported in other recent non-randomised studies[73-74, 117, 120] comparing axillary radiotherapy with axillary dissection.

### Axillary radiotherapy post-axillary dissection

In subgroup analysis of 15-year follow-up data from the DBCG 82 b&c randomised controlled clinical trials[25] conducted in high-risk patients, radiotherapy to the chest wall and regional lymph nodes (internal mammary nodes, peri-clavicular nodes, and the axilla) reduced the 15-year loco-regional failure rate from 51% to 10% ($p<0.001$) for patients with four or more positive nodes, and from 27% to 4% ($p<0.001$) for patients with one to three positive nodes.

In a small (n=76) randomised controlled trial[54] comparing axillary radiotherapy with no radiotherapy in patients who had undergone mastectomy and axillary node sampling, axillary radiotherapy was associated with a significant reduction in loco-regional recurrence at 10 years post surgery (65% vs 25%, $p<0.001$) .

A non-randomised study[45] reported that regional nodal irradiation reduced the rate of axillary relapse in patients with four or more positive lymph nodes at 8-year follow-up. No differences in survival or locoregional recurrence were reported in other non-randomised case series comparing axillary surgery plus radiotherapy with axillary surgery alone.

## OVERALL SURVIVAL

### Axillary dissection

Recent survival data are mainly derived from two randomised controlled clinical trials[23-24] that compared axillary dissection with surgery alone in patients undergoing mastectomy or breast-conserving surgery. The IBCSG[23] (n=473) compared surgery (either a total mastectomy or breast-conserving surgery) plus level III axillary dissection with surgery alone in women aged 60 years or older with clinically negative axillary nodes. At a median follow-up of 6.6 years, there was no significant difference in overall survival between groups. However, the findings must be interpreted with caution because approximately one third of patients in the non-axillary dissection group received breast radiotherapy.[23] Another small (n=76) randomised controlled trial[24] compared breast-conserving surgery plus axillary dissection with breast-conserving surgery alone in women aged 65–80 years with clinically negative axillary nodes who also received five years' tamoxifen treatment. No significant difference in overall survival between groups was observed.[24]

Further survival data are available from the 25-year follow-up of the NSABP04 randomised clinical trial.[22] A subgroup (n=1079) of women with clinically node-negative breast cancer, of whom 70% were aged over 50 years, were randomised to undergo either mastectomy plus axillary dissection, mastectomy alone (with axillary dissection if nodes became clinically positive; 68, or 18.6%, of the 365 in this group subsequently had positive ipsilateral nodes, removed by delayed axillary dissection), or mastectomy plus radiotherapy. Those in a second clinically node-positive subgroup (n=586) were randomised to undergo either mastectomy plus axillary dissection or mastectomy plus radiotherapy. *Lymph nodes* were found in a proportion of specimens removed in those designated mastectomy only, however no nodes were found in 65% of specimens in this group. In the mastectomy only group, the mean number of nodes removed was 2 (median 0), whereas in the mastectomy plus axillary dissection group, the mean was 18 (median 16).[125] At 25 years follow-up, there were no significant differences in survival rates between those who underwent axillary dissection and those who did not, for both the node-positive and node-negative subgroups.[22]

Available evidence suggests there is no difference between level I/II axillary dissection and level III axillary dissection with respect to survival outcomes. Two large randomised controlled clinical trials[19-20] with median follow-up intervals of more than 7 years reported no statistically significant difference in overall survival rates between patients who underwent level I dissection compared with level III dissection[20] and between patients who underwent level II dissection compared with level III dissection.[19]

### Axillary radiotherapy

A 2006 systematic review[49] of randomised *clinical trials* concluded that optimal postmastectomy radiotherapy (targeting the chest wall, axillary lymph nodes, and the supraclavicular fossa with or without the internal mammary lymph nodes) was associated with a 2.9% absolute increase in survival at follow-up intervals of up to 10 years. An earlier systematic review (2000)[52] reported that radiotherapy improved survival in the more recent trials and those which used current techniques.

A randomised controlled clinical trial[55] comparing breast-conserving surgery plus axillary radiotherapy with breast-conserving surgery alone in clinically node-negative women aged over 45 years reported significantly higher overall survival among the radiotherapy group at 5-year follow-up.

However, other trials did not report survival benefits. Fifteen-year follow-up data from two SBCSG randomised trials[58] comparing radiotherapy with *adjuvant chemotherapy* in high-risk patients (node-positive disease or a tumour diameter > 30 mm) showed no statistically significant difference in overall survival rates between groups. However, a non-significant survival trend in favour of chemotherapy was observed among premenopausal women (50% vs. 44%), and chemotherapy halved the risk of a second primary malignancy, compared with radiotherapy.[58] Axillary radiotherapy was not associated with a survival benefit at 12-year follow-up in a small (n=76) randomised controlled trial[54] comparing axillary radiotherapy with no radiotherapy in patients who had undergone mastectomy and axillary node sampling.

### Axillary radiotherapy versus axillary dissection

Twenty-five year follow-up data are available from the NSABP04 randomised clinical trial,[22] in which node-negative patients (n=1079) were randomised to receive either mastectomy plus axillary dissection, mastectomy alone (with axillary dissection if nodes became clinically positive), or mastectomy plus regional radiotherapy, and clinically node-positive women (n=586) were randomised to receive either mastectomy plus axillary dissection or mastectomy plus regional radiotherapy. *Radiotherapy* was not associated with a survival benefit in either the clinically node-negative or node-positive subgroup.[22]

Fifteen-year follow-up data from a randomised trial in women with clinically uninvolved lymph nodes[21] that compared axillary radiotherapy (n=332) with axillary dissection (n=326) reported no significant difference in overall survival

between treatment groups, despite an earlier difference in favour of axillary dissection. Other recent non-randomised studies[118-120] comparing radiotherapy with axillary dissection did not report a significant survival benefit associated with axillary radiotherapy.

A number of studies reported in a systematic review[4] demonstrated favourable survival rates among patients who underwent treatment regimens that included irradiation of the axilla. The degree to which the axillary radiotherapy component of therapy contributed to survival benefit is unclear. Axillary radiotherapy does not appear to show significant survival advantage;[22] however may be worthwhile in selected patients who are not candidates for axillary surgery.

### Axillary radiotherapy post-axillary dissection

In subgroup analysis of 15-year follow-up data from the DBCG 82 b&c randomised controlled clinical trials,[25] radiotherapy significantly improved survival, compared with observation, in high-risk patients who had undergone axillary dissection. This benefit was observed for patients with 1–3 positive nodes (57% vs. 48%, p=0.03) and four or more positive nodes (21% vs. 12%, p=0.03).[25]

## ADVERSE EVENTS

### LYMPHOEDEMA

A significant potential side effect after surgery and/or radiotherapy is secondary *lymphoedema*, affecting approximately 20% of breast cancer survivors.[126] Axillary dissection is associated with increased risk of lymphoedema.[2, 127] In the IBCSG trial[23] in patients aged 60 years and over, axillary dissection did not result in a significantly increased mean arm circumference or lymphoedema rate, compared with observation. Axillary dissection resulted in a numerically higher rate of early lymphoedema than four-node sampling (4% versus 2%) in a randomised controlled clinical trial[53] for which 5-year follow-up data are available. Swelling resolved over time in the sampling group and, at 3 years after surgery, patients who had undergone sampling showed significantly smaller forearm girth than those who had undergone axillary dissection.[53] The results of the axillary clearance arm of the RACS SNAC trial provide valuable information regarding lymphoedema rate noted prospectively and the timing of onset.[128]

Radiotherapy (administered as clinically indicated) resulted in a similar rate of lymphoedema as axillary dissection in the randomised controlled clinical trial[8] comparing level III axillary dissection with axillary node sampling. *Radiotherapy* was associated with mild-to-moderate lymphoedema in 6% of patients in a small randomised controlled clinical trial[54] that compared radiotherapy with observation following *mastectomy* and axillary node sampling in women with node-positive breast cancer. Some non-randomised comparative trials reported higher rates of lymphoedema among patients who received radiotherapy compared with those who underwent axillary dissection alone.[44, 115, 120]

### SHOULDER MOVEMENT

Axillary dissection resulted in higher rates of arm restriction (39% versus 15%) and pain (23% versus 7%) at the first postoperative visit, compared with observation in the IBCSG trial.[23]

Axillary dissection, but not node sampling or radiotherapy, was associated with a slight reduction in shoulder movement at 3-year follow-up in a randomised controlled trial[53] comparing level III axillary dissection with axillary node sampling, in which selected patients received radiotherapy (n=54).

Radiotherapy following axillary sampling was associated with a significantly greater reduction in range of shoulder flexion than node sampling alone in the same node-sampling randomised controlled trial.[53] Radiotherapy also

reduced lateral and medial shoulder rotation at 6 months, compared with no radiotherapy, but this improved over time. Patients who underwent radiotherapy also showed reduced shoulder muscle power persisting up to 1 year, but no effect persisted at 3 years.[53]

## OTHER ADVERSE EVENTS

In one study,[73-74] pneumonitis was reported in 4% of those who receive radiotherapy to the breast and regional lymphatics, with a numerically higher rate among those who also received *chemotherapy*. Brachial plexus neuropathy occurred in 1% of patients who received radiotherapy, but resolved completely within 30 months.[73]

## LONG-TERM ADVERSE EVENTS

Findings from the IBSCG trial[23] suggest that the increase in adverse effects associated with axillary dissection, compared with no dissection, do not persist long term.

Compared with level I or I/II dissection, level III dissection did not result in increased long-term morbidity such as oedema, arm pain, motor function, social functioning or pectoralis major muscle atrophy in two randomised *clinical trials*.[19-20]

## QUALITY OF LIFE

Data on quality of life were not consistently reported in trials and studies of axilla management.

### Axillary dissection

The IBCSG study[23] reported a reduction in arm-related quality of life, compared with no axillary surgery. However, at 6-year follow-up, there was no significant difference in quality of life between patients who underwent axillary dissection and those who underwent breast surgery without axillary dissection.[23]

## Strengths and weaknesses of evidence

Eleven randomised controlled trials were identified, with information on both staging and treatment of the *axilla*. Some of these trials provided long-term data (maximum 25 years follow-up[22]).

Much of the information on the management of the axilla was from non-randomised trials including studies on diagnostic accuracy, prognostic studies, observational studies and case series. Most of these trials were retrospective and were often small, with varied topics and results reported.

## Unanswered questions

The following important clinical questions cannot be answered adequately based on currently available data. Topic areas for these unanswered questions include:

- What is the optimal use of magnetic resonance spectroscopy, MRI, PET and *ultrasound* in staging the axilla?
- How should prognostic tools be used to predict further nodal involvement?
- What is the significance of micrometastases and isolated tumour cells?
- What is the optimal management for patients with a positive finding on sentinel node biopsy?
- What quality of life issues are associated with management of the axilla?
- What is the optimal use/duration of *radiotherapy* following axillary dissection?

## Ongoing and additional trials or studies

A number of ongoing trials are investigating the management of the *axilla* for early breast cancer:

- accuracy of *sentinel node biopsy* in a randomised controlled trial comparing sentinel node *biopsy* versus axillary clearance for multi-focal and larger breast cancers (SNAC2)[129]
- a phase III randomised controlled clinical trial assessing complete axillary *lymph* node dissection versus axillary *radiotherapy* in sentinel lymph node-positive women with operable *invasive breast cancer* (EORTC-10981-AMAROS, NCT0001461)[130]
- a randomised trial of axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel node (CDR0000339581/IBCSG-23-01/EU-20319/NCT0007229329).[131]

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### Membership of the NBOCC *Axilla* Working Group

This guideline was developed by a multidisciplinary working group convened by NBOCC.

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### External Review

NBOCC acknowledges those who gave their time to provide comment on the draft guideline recommendations as part of the external review process.

Full details of trial results are provided in the document *Management of the axilla for early breast cancer: a systematic review*, which can be accessed via the Cancer Australia website: http://canceraustralia.nbocc.org.au/


## Additional information


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* In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.