Management of the axilla in women with breast cancer

First edition
This document addresses the issue of management of the axilla in early stage breast cancer. It has been compiled with multidisciplinary input from the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists (FRO, RANZCR), the Breast Section of the Royal Australasian College of Surgeons, the Medical Oncology Group of the Royal Australasian College of Physicians and the Breast Cancer Network of Australia.

Principal authors:
Dr Susan Pendlebury, Radiation Oncologist
Mr David Speakman, Breast Surgeon

Contributing authors:
Professor Alan Rodger, Radiation Oncologist
Dr Martin Borg, Radiation Oncologist
Dr Graeme Morgan, Radiation Oncologist
and other members of the National Breast Cancer Centre/FRO, RANZCR Advisory Group
Mr Michael Henderson, Breast Surgeon
Mr James Kollias, Breast Surgeon
Mr Owen Ung, Breast Surgeon
Dr Raymond Snyder, Medical Oncologist
Ms Lyn Swinburne, Consumer Representative, Breast Cancer Network of Australia

National Library of Australia Cataloguing-in-Publication data:
Management of the axilla in women with breast cancer
First Edition

ISBN 1 876319739
616.99449

© 2001
iSource National Breast Cancer Centre
PO Box 572
Kings Cross NSW 1340
phone: +61 2 9334 1700
fax: +61 2 9326 9329
e-mail: directorate@nbcc.org.au

The iSource National Breast Cancer Centre is funded by the Australian Commonwealth Government
Important Notice

This document is a guide to appropriate practice, to be followed subject to the clinician’s judgement and the woman’s preference in each individual cases.

The guidelines are designed to provide information to assist decision making and are based on the best evidence available at the time of publication.
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important notice</td>
<td>i</td>
</tr>
<tr>
<td>List of abbreviations</td>
<td>1</td>
</tr>
<tr>
<td>Foreword</td>
<td>3</td>
</tr>
<tr>
<td>Executive Summary</td>
<td>5</td>
</tr>
<tr>
<td>Management of the Axilla in Women with Breast Cancer</td>
<td>7</td>
</tr>
<tr>
<td>Aims of this document</td>
<td>7</td>
</tr>
<tr>
<td>Balancing the risks and benefits of axillary dissection and axillary irradiation</td>
<td>8</td>
</tr>
<tr>
<td>The impact of treating the axilla on survival and axillary recurrence: the evidence</td>
<td>10</td>
</tr>
<tr>
<td>Staging the axilla: advantages and alternatives</td>
<td>16</td>
</tr>
<tr>
<td>Clinical practice recommendations</td>
<td>21</td>
</tr>
</tbody>
</table>

## Appendix

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix I</td>
<td>Axillary surgery: definitions</td>
<td>25</td>
</tr>
<tr>
<td>Appendix II</td>
<td>Risks of axillary dissection and irradiation</td>
<td>29</td>
</tr>
<tr>
<td>Appendix III</td>
<td>Sentinel node biopsy in breast cancer</td>
<td>33</td>
</tr>
<tr>
<td>Appendix IV</td>
<td>Technical aspects of radiation therapy to the axilla</td>
<td>37</td>
</tr>
</tbody>
</table>

## References

| References | 39 |
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluoro deoxy glucose</td>
</tr>
<tr>
<td>FRO</td>
<td>Faculty of Radiation Oncology</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>ICBN</td>
<td>Intercostobrachial nerve</td>
</tr>
<tr>
<td>ICRU</td>
<td>International Commission on Radiation Units and Measurements</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NBCC</td>
<td>iSource National Breast Cancer Centre</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NSABP</td>
<td>National Surgical Adjuvant Breast and Bowel Project</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>RANZCR</td>
<td>Royal Australian and New Zealand College of Radiologists</td>
</tr>
</tbody>
</table>
Foreword

This document has been developed to support recommendations about the management of the axilla in women with early stage breast cancer. It encompasses recommendations on both axillary surgery and axillary irradiation and the need to consider axillary management within a multidisciplinary framework in order to optimise treatment decisions. The document grew out of a need identified by the NHMRC National Breast Cancer Centre (NBCC) Consumer Advisory Group for recommendations for clinicians about surgery and radiotherapy to the axilla in relation to lymphoedema. The information contained within this document is evidence-based. Recommendations for practice supported by the evidence were agreed at a multidisciplinary consensus conference in 1998. Representatives involved in the consensus conference included radiation oncologists, surgeons, medical oncologists and consumers.

The resulting document provides women and clinicians with information about indications for axillary surgery and axillary irradiation, and is aimed at both minimising the risk of recurrence and limiting the impact of such interventions on the occurrence of lymphoedema and other morbidities.

The project team involved in the preparation of this document reflects the interest of the NBCC and its Consumer Advisory Group in the development of axillary recommendations – an interest shared by the many oncological disciplines involved in the treatment of breast cancer. Representatives nominated from the Royal Australasian College of Surgeons Breast Section, from the RANZCR Faculty of Radiation Oncology and from the Royal Australasian College of Physicians (Medical Oncology Group) have made significant contributions.

The Centre is grateful to all those who have contributed their time and advice. The document will, in time, be updated to incorporate new evidence on the optimal management of the axilla in the treatment of breast cancer.
Executive summary

Based on a review of the available literature, there is evidence that:

- Management of the axilla should be determined by a multidisciplinary team in discussion with the woman (Level III).\textsuperscript{54}

- For women with early breast cancer, a minimum Level I and II axillary node dissection should be offered as the standard procedure to reduce the risk of regional recurrence (Level II).\textsuperscript{5,7}

- Axillary dissection can be omitted for some women:
  - women diagnosed with DCIS\textsuperscript{55} (Level III); and
  - selected patients (Level IV).

- Axillary irradiation will be the preferred method of treatment for some women (Level III):\textsuperscript{6,36,56}
  - elderly patients or those with other serious health problems; and
  - women who do not wish to have surgery.

- Some women will require axillary irradiation following axillary surgery (Level IV):
  - women who have surgical or pathological evidence of remaining axillary disease following dissection; and
  - who have undergone less than axillary dissection, eg formal sample or sentinel node biopsy, which is positive for malignancy.

- Coordination of trials of sentinel node biopsy across Australia should be undertaken as a matter of priority (Level IV).

There is currently no Level I or II evidence to confirm or refute a benefit of:

- axillary dissection in prolonging survival;
- an impact of axillary irradiation on mortality from breast cancer; or
- axillary irradiation in women with breast cancer based solely on reported extranodal spread.

There are no Level I or II studies which compare sentinel node biopsy with formal axillary dissection.
Executive summary

Management of the axilla in women with breast cancer
Management of the Axilla in Women with Breast cancer

Aims of this document

This document has two aims: to examine critically the evidence governing management of the axilla; and to provide a guide to current optimal practice and the way in which new practices may be incorporated. The literature was examined up until mid-2000. This document has been informed by reviews of the available evidence and recommendations by expert groups, and the evidence has been rated according to the system developed by the US Preventive Services Task Force (see Appendix 2).

Level I evidence (where evidence is obtained from a systematic review of all relevant randomised controlled trials) represents the gold standard. However, Level I evidence is not available for all areas of practice and for some recommendations the working party considered it appropriate to base recommendations on other levels of evidence.

Most women diagnosed with invasive breast cancer currently undergo axillary dissection.\textsuperscript{1,2,3} Some of these women will also receive axillary irradiation.

Axillary dissection is used to stage the cancer to determine further treatment.\textsuperscript{4} The current rationale for axillary treatment, by dissection or irradiation, is that it is used to reduce the risk of axillary recurrence\textsuperscript{5} and possibly increase survival.\textsuperscript{6,7} Definitions and technical descriptions of these techniques are provided in Appendices II and IV.\textsuperscript{8}

However, these techniques have a number of side effects with particular concern focusing on lymphoedema – both together and separately. It is clear that the lymphoedema of the arm is more prevalent in women who have had both axillary dissection and axillary irradiation following a diagnosis of breast cancer.\textsuperscript{9}
There is considerable confusion among women about the role of axillary dissection and axillary irradiation. There is also evidence of considerable variation in practice across Australia.\(^1\)

The recommendations about optimal practice contained in this document are intended to both assist clinicians and form the basis of information for women.

**Balancing the risks and benefits of axillary dissection and axillary irradiation**

There are two reasons for undergoing axillary dissection and/or axillary irradiation:

1. **Treating disease in the axilla**

   Cancer cells can travel from the breast through the lymph system to the axillary nodes. If the cancer has already spread to the axillary lymph nodes at diagnosis, surgery and radiotherapy to the breast alone may not control the disease in the axilla. The woman’s chances of survival are reduced and there may be recurrence of the disease in the axilla.\(^6\)

   Axillary dissection and axillary irradiation are used to treat any disease that may have potentially spread to the axilla.

2. **Staging the disease**

   Axillary dissection is also used to assess whether the disease has spread to the axillary lymph nodes and, if so, to how many nodes. This information may be used to determine what type of systemic therapy is indicated, whether irradiation is indicated and to what extent. It also allows the most accurate prognosis.\(^4\)

   There is something of a paradox in the current approach to axillary dissection. Only women who transpire to have positive lymph nodes have required treatment of the axilla. However, at this time, the best strategy for determining complete lymph node status is through axillary dissection. This means that some women with negative lymph nodes and who will not benefit directly from treating the axilla will receive axillary dissection for staging purposes only.
The consequence of uncontrolled disease in the axilla

Regional axillary recurrence

A recurrence of breast cancer in the axilla carries significant risks to the woman. Risks include a mass in the axilla that may be difficult to treat; brachial plexus infiltration; lymphoedema; and, rarely, axillary skin ulceration. The risk of such problems in the untreated axilla varies with tumour size, from about 10% for tumours less than 1 cm to 33% for tumours greater than 2 cm. A large trial of early breast cancer estimated that expectant management of the axilla would result in an incidence of uncontrolled axillary disease in about 20% of cases. Both this trial and another have demonstrated the importance of treating the axilla. Where the axilla was selectively excluded from treatment, both trials showed an increased risk of locoregional recurrence.

Lymphoedema is an important side effect of axillary treatment and of axillary recurrence. Although rarely simple to manage, it is easier to manage in an axilla where the disease is controlled rather than uncontrolled.

Side effects of axillary dissection and axillary irradiation

There are a number of major side effects of axillary dissection and axillary irradiation. These are described in detail in Appendix II. Risks associated with axillary dissection include seromas; wound infection; damage to motor nerves; numbness and paraesthesia; reduced shoulder mobility and stiffness; and lymphoedema. The side-effects of axillary irradiation include lymphoedema; reduced shoulder mobility or arm movement restrictions; and, much more rarely, rib fracture, brachial plexus damage, pneumonitis, axillary blood vessel damage and sarcoma formation.
Lymphoedema is one of the most common and therefore significant side effects of an intervention to the axilla, with either radiotherapy or surgery. The incidence of ‘clinically obvious’ lymphoedema associated with axillary dissection alone is approximately 7%.9 The incidence of lymphoedema associated with axillary irradiation alone is similar. However, when both dissection and irradiation are given, more recent studies report rates of around 30%. There is randomised trial evidence that lymphoedema rates for axillary sample plus irradiation are not different from those for either modality alone.12

The impact of treating the axilla on survival and axillary recurrence: the evidence

Does axillary dissection increase survival from breast cancer?

The benefits of axillary dissection in prolonging survival are unclear. Studies have reported different effects on survival, and most have some methodological flaws. For example, the NSABP B-04 trial5 found that there was no difference in survival between women who had simple mastectomy and those who had radical mastectomy (including axillary dissection). However, 33% of women in the non-dissected group had undergone some form of limited axillary surgery and the power of the study may have been insufficient to demonstrate a clinically significant difference between the groups.

Other studies have found overall long term benefits in survival when axillary dissection was carried out.7,13,14 For example, a study by Cabanes7 et al. – of lumpectomy plus breast and axillary irradiation without axillary dissection, versus lumpectomy and breast irradiation with axillary dissection – showed a small but significant improvement in survival in women who had axillary surgery (92.6% versus 96.6%, p = 0.014).7 However, interpretation of these results is difficult since a significant proportion of the axillary dissection group received adjuvant systemic therapy based on their nodal status.
Two other studies, the Guys Hospital breast conservation study\(^{13}\) and the Edinburgh study comparing a radical mastectomy with a total mastectomy plus radiotherapy,\(^{14}\) found significantly decreased survival for treatment groups that had a higher rate of locally uncontrolled disease. Both concluded overall long-term benefits in survival when axillary dissection was compared to no intervention or radiotherapy to the axilla.

In summary, the data suggest that axillary dissection may have an impact on survival, although the evidence remains insufficient.

**Does axillary dissection reduce axillary recurrence?**

*Axillary dissection reduces the risk of axillary recurrence (Level II).* The best evidence for this comes from the NSABP B-04 trial,\(^{5}\) which reported 10-year axillary recurrence rates of only 1% (node negative) and 3% (node positive) for women who had undergone axillary lymph node dissection at mastectomy, compared to more than 17% in women who had not (Level II). Other studies have shown that axillary recurrence is inversely related to the number of nodes removed from the axilla.\(^{15,16}\)

**Does axillary irradiation influence survival from breast cancer?**

*The impact of axillary irradiation on mortality from breast cancer remains unclear.* Although Overgaard\(^{17,18}\) showed a survival benefit for postmastectomy radiotherapy which included the axilla, the patients included in that study were high risk T 3-4 and node positive. The surgical management of the axilla in that trial was also different from most Australian centres, in that the mean lymph node yield was less in the Danish trial. Another trial has shown a trend towards improved survival\(^{19}\) (Level II). However, in these three trials the postmastectomy radiotherapy included chest wall, axillary, supraclavicular and internal mammary node irradiation. Indeed, given that all nodal areas were irradiated in these trials, it is impossible to isolate one area of treatment as being solely responsible for their identified survival improvements.
However, no other trial, overview\textsuperscript{20} or meta-analysis has demonstrated a survival benefit.

At this time there is therefore no Level I evidence to conclude that post-operative radiotherapy to the axilla provides a survival benefit.

**Does irradiating the axilla reduce axillary recurrence?**

Axillary irradiation reduces axillary recurrence (Level I)\textsuperscript{20} and can therefore be considered an alternative to axillary dissection.

In an overview of randomised trials, the Early Breast Cancer Trialists' Collaborative Group\textsuperscript{20} demonstrated that radiotherapy reduced the locoregional relapse rate by about two-thirds, from 19.6\% to 6.7\%. This was independent of the type of axillary surgery or nodal status, and included breast-conserving surgery and mastectomy.

Axillary irradiation may be added to axillary dissection in some cases where women are identified as being clearly at risk of axillary recurrence, especially where there is evidence of disease remaining after dissection. In these situations, axillary irradiation may confer additional benefits over dissection alone, in controlling axillary disease and preventing ensuing symptoms.

The benefit of axillary radiotherapy in different subgroups needs to be carefully considered, as the extent of the benefit for various subgroups will differ depending upon their risks and must be balanced against potential morbidity.
Axillary irradiation following dissection in women with limited nodal involvement

Relevant data is provided by extrapolating results from several large randomised trials\textsuperscript{21,22,23} which compared breast-conserving therapy and mastectomy. The trial findings suggest that there may be little benefit from adding axillary irradiation among women who have had axillary dissection and have only a small number of involved lymph nodes.

For example, the NSABP B-06 trial\textsuperscript{21} reported that 90\% of patients had less than four lymph nodes positive in a dissected axilla. Local axillary relapse in this entire series is low, at around 1–3\%. It is unlikely that the addition of radiotherapy will confer much benefit where rates of relapse are already very low.

This conclusion is supported by a strong body of retrospective data\textsuperscript{6,22,23}. Data from the Mayo Clinic suggest isolated locoregional recurrences (ie recurrences on the chest wall or lymphatic areas) of only around 8\% with less than four lymph nodes involved.\textsuperscript{24} Similarly, Fowble et al.\textsuperscript{25} suggest that isolated locoregional recurrences occur in 7\% of women with limited nodal involvement. Of the 634 patients analysed by Fowble et al.,\textsuperscript{25} only 1.3\% recurred in the axilla alone and another 1.3\% in multiple sites that included the axilla – that is, the total axillary recurrence rate was only 2.6\%.

Fisher\textsuperscript{15} et al. analysed patterns of recurrence in 320 patients who had been treated for Stage II or III breast cancer with surgery and chemotherapy without locoregional radiation therapy. They found 21 isolated axillary recurrences (6.6\%) at a median follow-up of 77 months, and concluded that the number of axillary nodes involved was not predictive of recurrence.
Axillary irradiation following dissection in women with greater lymph node involvement or remaining disease in the axilla

While the above data suggest that there is little to be gained by axillary irradiation in women with only a small number of involved lymph nodes, it seems that there may be benefit from the addition of radiotherapy when it is likely that there is remaining disease in the axilla. This included cases where the surgeon believes that macroscopic disease was left behind or transected, or where the pathologist indicates positive margins.

The addition of axillary irradiation with greater nodal involvement is more controversial than with limited nodal involvement. When there is greater nodal involvement, local relapse rates will be increased where surgery is the sole treatment. For example, data from the Mayo Clinic suggest isolated locoregional recurrences at three years of 14% among women with 4–7 positive nodes and 22% for women with eight or more positive nodes. Similar data have been reported by Fowble et al. However, not all of these relapses are axillary. Most studies have shown at least 50% to be on the chest wall. These studies are non-randomised.

The three randomised trials noted above, showing an improvement in survival in high risk disease for patients irradiated to the entire lymphatics and chest wall, also showed a reduction in locoregional relapse from 32% to 9% at 10 years. Although the distribution of local relapses was not given, more than half were on the chest wall. Even in patients with heavy nodal involvement, axillary recurrences remain uncommon. Not all analyses have demonstrated increased axillary relapse rates with increasing numbers of involved nodes.

However, it is important to consider the role of axillary irradiation in patients at high risk of local recurrence. Not all axillary recurrences can be salvaged. It is particularly difficult to salvage axillary recurrence with radiotherapy where the axilla has been previously selectively excluded from the chest wall and supraclavicular fossa volume. The prevention of recurrence may therefore be a preferable option, albeit carrying the cost of increased risks of lymphoedema.
Axillary irradiation following dissection in women with extranodal spread

The significance of axillary extranodal spread in breast cancer has been a controversial issue. Studies have examined the effects of extranodal spread on both survival and local recurrences compared with patients in the same series who have no extranodal spread. All are retrospective reviews of single institution data. Most have demonstrated significant reductions in overall survival in patients with extranodal spread of disease, and one study showed a non-significant trend (Level III).

In examining the risks of locoregional recurrence, some of these studies have demonstrated increased relapse rates. They looked specifically at any differences between focal and extensive extranodal spread and found no difference in rates of local relapse. Only two studies have examined the sites of local relapse in patients with axillary extranodal spread. Both have demonstrated increased chest wall recurrences but no significant increase in axillary recurrence rates. The axillary recurrence rate in both studies was 7%. While this figure is higher than reported axillary relapse rates in patients with comparable numbers of involved lymph nodes without extranodal spread, it was not significantly higher in the studies reported. There remains no Level I or II evidence to support axillary irradiation in patients with breast cancer based solely on reported extranodal spread.

Is axillary irradiation as effective as axillary dissection in local control?

There are data (Level II) reporting no difference in outcome between axillary dissection and radical radiotherapy to the undissected axilla in clinically node negative axillae. Patient factors such as individual preference, performance status and age should be taken into account. Differences in morbidity patterns should be also considered.
Staging the axilla: advantages and alternatives

Surgical staging of the axilla is currently the usual practice for the majority of women, as it provides prognostic information and data upon which major treatment decisions are made. Although several prognostic indices have been developed to date, most rely on knowledge of the nodal status. Axillary lymph node status is the most powerful single variable in the estimation of prognosis for primary breast cancer. Prognosis is related to the number of axillary nodes which contain metastases; this relationship applies to both disease-free interval and to survival.

The absolute benefit that any individual patient will derive from adjuvant systemic therapy depends on an accurate assessment of her individual risk of relapse. Currently, the best indicator of this is lymph node status. For women considering entry to systemic therapy clinical trials, some require minimum numbers of lymph nodes to have been examined.

Systemic adjuvant therapy can provide a survival benefit. However, chemotherapy in particular is associated with major side effects. For those women in whom it is unlikely that the disease has spread, there will be little advantage in systemic adjuvant therapy but the potential for considerable morbidity from the side effects.

The number of nodes involved is an important selection factor for adjuvant systematic therapy, since the benefits of systemic therapy are expressed as a reduction in risk. The probability of lymph node involvement is related directly to the size of the primary tumours. Larger tumours are more likely to have metastasised to axillary lymph nodes than smaller ones. However, even in small primary tumours (up to 10 mm), the risk of nodal metastases is in the order of 10%, and for these patients identification of the involved lymph nodes will alter both their prognosis and the adjuvant therapy offered. It is important to note that there is an increase in the proportion of women with breast cancer who may not benefit from systemic adjuvant therapy. Screen-detected cancers, which tend to be small and associated with an excellent prognosis, are becoming increasingly more common. Adjuvant systemic chemotherapy has little role in this group of patients.
There is evidence that chemotherapy will not substitute for inadequate local treatment\(^{21}\) (Level I) and so may not be effective against all the cells that may have spread to the axilla.

**Alternatives to axillary dissection for staging**

At this time, axillary dissection remains the best available technique for staging the axilla to provide full qualitative and quantitative information.

**Non-operative approaches**

Surgical staging of the axilla has remained the gold standard because no reliable non-operative alternative has yet proven as effective. Clinical examination misses 30–75% of involved lymph nodes and even when lymph nodes are palpable at the time of presentation, nodal metastases will be confirmed on histological examination in less than 50% of cases.\(^{46,47}\) Mammography is a sensitive method of detecting large axillary lymph nodes, but its specificity is severely limited. Careful ultrasound of the axilla supplemented with colour Doppler improves both sensitivity and specificity, but not to an extent that justifies its routine use. Other nodal imaging techniques which have been investigated with limited success include nuclear scanning and labelled antibody scanning. Magnetic resonance imaging (MRI) examination of the axilla has not confirmed its initial promise and cannot be considered at the present time to be sufficiently sensitive and specific. Fluoro deoxy glucose (FDG) positron emission tomography (PET) has shown promising early results, with a sensitivity of 75% and specificity of 90%. However, small volume nodal disease is unlikely to be accurately staged using present PET technology, which is expensive and not widely available.
Axillary sampling

A formal axillary sample, as described by Steele et al. and which provides a minimum of four nodes, is an adequate means of qualitatively establishing whether the axilla is involved. Many argue that it is not an easily reproducible technique. It does not provide total quantitative data in patients with involved axillae. A randomised trial of axillary clearance versus a four-node lower axillary sample (with axillary irradiation in the case of a positive sample) shows comparable axillary control rates (Level II).

Axillary sampling may be adopted by those comfortable with the technique where the patient is known to be least likely to have involved nodes (eg small low grade tumours) and the extent of nodal involvement is unlikely to influence the choice of systemic therapies (especially in the elderly). If the sampled lymph nodes contain tumour deposits, further treatment of the axilla (ie radiotherapy, further surgery) is indicated. Axillary sampling carries a low rate of arm morbidity.

Sentinel node biopsy

Although no formal clinical trial results are yet available, the most promising alternative to axillary dissection for staging is sentinel node biopsy. This technique can detect a positive axilla but does not represent adequate treatment of it. It constitutes a very focused sample based on identifying the sentinel node, ie the first node that drains the site of the primary lesion. If this node does not contain any evidence of cancer, then the likelihood that other nodes in the breast are involved is extremely small (approximately 5–7% in experienced hands).

Sentinel node biopsy is discussed in detail in Appendix III. There is some evidence (see Appendix III) that as currently practised, it may not always be possible to find the sentinel node and that in a small number of cases (5–7% in experienced hands) other positive nodes will be present with a negative sentinel node. In well reported larger series, however, sensitivity, specificity and accuracy are all in excess of 90%, The technical difficulty and the considerable learning curve of the procedure cannot be underestimated. A recent report has found a significant reduction in the accuracy of the procedure when inexperienced versus experienced operators were analysed.
There is currently no randomised data available comparing sentinel node biopsy with formal axillary dissection. Those trials are still in progress internationally. However, there is a recent report\(^5\) prospectively comparing sentinel node biopsy and four-node positive sampling. The Nottingham Breast Unit examined 150 routine axillary node samples to see whether the sentinel node was removed. In 76% of cases, the sentinel node was excised as part of a routine axillary node sample. In 14 cases, the sentinel node was not identified. In five patients, the sentinel node was found to be false negative. However, no patient was found to be under- or down-staged by the routine axillary node sample. It was concluded that the sentinel node biopsy was an acceptable alternative to sampling, but of no significant advantage over a routine sample.

As with the four-node axillary sampling, a positive sentinel node biopsy simply denotes a positive axilla – it does not represent adequate treatment of the axilla. Further treatment to the axilla is required for patients with positive sentinel nodes. This can be with formal axillary dissection or with radiation therapy. The choice will almost certainly depend upon local treatment protocols and patient selection factors (e.g., age). The lymphoedema rates for radiotherapy following a positive sampling procedure are equivalent to those of a dissected axilla without radiotherapy.\(^1\) It would be expected to be similar for radiotherapy following a positive sentinel node biopsy.
Clinical practice recommendations

These recommendations are derived both from the previous discussion of the evidence and from a multidisciplinary consensus conference in which draft evidence-based statements were prepared and discussed. It was agreed that the recommendations represent both the evidence and best practice in relation to the management of the axilla.

1 Management of the axilla should be determined by a multidisciplinary team in discussion with the patient (Level III).54

Patient management is optimal in clinical situations where multidisciplinary communication is greatest. There are several reasons why multidisciplinary communication is particularly important in the management of the axilla. For example, in determining whether axillary irradiation is required following axillary dissection, the surgical description of the operative findings is critical. A description of lymph nodes being enmeshed around axillary blood vessels and needing to be dissected free, almost always denotes macroscopic residual disease. This may not be evident from the pathology report. The nature of pathological handling of the axillary contents makes orientation of the axillary specimen and description of margins extremely difficult.

Likewise, for some patients, the preferred method of treatment may be radiotherapy alone or no treatment. Close communication between the surgeon and the radiation oncologist is required to manage such patients. For example, in an elderly frail patient with a purely tubular carcinoma, the decision to ‘observe’ the axilla rather than use surgery or radiation therapy should be made jointly between the woman, her surgeon, her radiation oncologist and her medical oncologist.
Given that the management of the axilla always involves a balance of the potential costs and benefits of treatment, the woman must always be fully informed of and participate in the decision. She should be provided with information about the benefits of axillary dissection and irradiation in reducing the risk of local recurrence and possibly increasing survival. She should also be advised about the value of staging information in determining the best systemic adjuvant treatment if required. She should also be fully informed about the potential side effects of axillary dissection and irradiation, particularly lymphoedema.

2 For women with early breast cancer, a minimum level I and II axillary node dissection should be offered as the standard procedure to reduce the risk of regional recurrence (Level II).\(^5,7\)

There is evidence that axillary dissection reduces the risk of regional recurrence.\(^5,7\)

3 Axillary dissection can be omitted for some women.

The omission of axillary dissection can be considered for women in whom it is likely that the risks will outweigh the benefits; however, the decision to omit axillary dissection should be discussed fully with the woman. These patients include:

- **Women diagnosed with ductal carcinoma in situ:**
  A number of studies have demonstrated that the rate of axillary metastases in women with DCIS is less than 1%.\(^5,5\) Axillary dissection should be omitted in these patients (Level III).

- **Selected patients:**
  In selected patients in whom the result of axillary dissection would be unlikely to influence the decision to use adjuvant systemic therapy, axillary dissection may be omitted. This may include frail, elderly women. Although not subjected to any completed formal controlled trial, management without axillary surgery may be appropriate in such
patients with small low grade tumours, no palpable axillary disease and very close clinical follow-up (Level IV).

4 **Axillary irradiation will be the preferred method of treatment for some patients (Level III).**

Evidence suggests that axillary irradiation is as effective as axillary dissection in preventing local recurrence (Level III).\(^6,36,56\) For some patients, axillary irradiation will be the preferred method of axillary management. These patients include:

- **Elderly patients or those with additional serious health problems:** Radiotherapy is the appropriate alternative for these women in whom additional surgery should be avoided.
- **Patient choice:** Some patients may not wish to have further surgery.

5 **Some patients will require axillary irradiation following axillary surgery (Level IV).**

Some women at high risk of axillary recurrence will require both axillary dissection and axillary irradiation. This particularly includes women who have surgical or pathological evidence of remaining axillary disease following dissection.

Where women have undergone less axillary surgery than a dissection (a formal sample or sentinel node biopsy, for example) and this procedure is positive for axillary malignancy, they will require further axillary treatment and may elect for the treatment to be with radiotherapy rather than further surgery.

6 **Coordination of trials of sentinel node biopsy across Australia should be undertaken as a matter of priority (Level IV).**

Ideally, only those women with positive nodes should receive axillary dissection. However, there are currently no established alternatives for determining lymph node status other than axillary dissection.
The most promising alternative is sentinel node biopsy. This is currently available in Australia only on an experimental basis; different approaches are being used and a number of problems with the technique have been identified. The proposed schema for a clinical trial in Australia is that patients be randomised to either a standard axillary dissection or to a sentinel node biopsy. If the sentinel node were negative, they would not receive further axillary treatment. A positive sentinel node biopsy would be followed by a formal axillary dissection.

A nationally coordinated, controlled trial would provide information about the possible role of sentinel node biopsy relatively quickly. It would ensure that women are not provided with this treatment outside of clinical trials and that appropriate quality assurance is achieved.
Appendix 1

Axillary surgery – definitions

Definitions of axillary dissection

There is a wide variation in the extent of axillary dissection in the management of breast cancer. It ranges from no surgical intervention at all, to the sampling removal of a few lower nodes, to a specific sentinel node biopsy, to an exhaustive complete clearance to the apex of the axilla. This variation has largely been due to a number of differing beliefs about the amount of nodal tissue required for staging, and about the benefits of a clearance procedure.

In summary, the anatomical boundaries of the axilla are:57

<table>
<thead>
<tr>
<th>Anterior wall</th>
<th>Pectoralis major and minor muscles subclavius, clavipectoral fascia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial wall</td>
<td>Serratus anterior muscles/cheast wall</td>
</tr>
<tr>
<td>Lateral wall</td>
<td>Humerus (medial side), brachialis muscle</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>Latissimus dorsi, teres major and subscapularis muscles.</td>
</tr>
<tr>
<td>Base</td>
<td>Axillary fascia</td>
</tr>
<tr>
<td>Apex</td>
<td>Formed by outer border of first rib, clavicle and scapula</td>
</tr>
</tbody>
</table>

In order to facilitate communication and uniformity of approach, the axilla can be conveniently divided into three levels based around the pectoralis minor muscle. This leads to the definitions of level I, II and III clearance as outlined below:58
Level I dissection: clearance from the lateral/lower border of pectoralis minor

This may also be described as a ‘lower axillary dissection’. It includes all tissue inferior to the axillary vein and extends laterally to the point where the axillary vein crosses the tendon of latissimus dorsi. The rest of the dissection is limited by the axillary fascia and the chest wall.

Level II dissection: clearance from the medial/upper border of pectoralis minor

This dissection includes all of the level I tissue, plus those deep to the body of the pectoralis minor muscle. Essentially, it simply extends a level I dissection to the medial border of pectoralis minor.

The pectoralis minor muscle may be either divided or retracted to gain access to this region. No significant difference in morbidity has been detected using either technique.

Level III dissection: clearance from the axillary apex

This involves the complete removal of all nodal tissue from the axilla. The dissection extends superomedially to the lateral border of the first rib and costoclavicular (Halsted’s) ligament.

Node retrieval

There is a wide variation in the number of glands harvested from any individual nodal basin. For example, in the axilla, complete clearance has been reported as yielding as few as eight nodes and as many as sixty in series from one institution.58
Appendix I

Management of the axilla in women with breast cancer

Average lymph node harvests:60,61,62,63

- Level I alone 9–13
- Level II alone 5–9
- Level III alone 2–6

The median nodal retrieval in Australia is 14 lymph nodes.64,65

Axillary sampling

Axillary sampling is a non-anatomical dissection. This technique removes significantly less nodal tissue than the clearances described above. However, there are variations in the amount of nodal tissue retrieved. In its simplest form it can be described as the removal of lymph nodes from the lower axilla. A limited resection of the axillary tail of the breast and adjacent tissue containing lymph nodes is performed.60,66 The more elaborate descriptions of this procedure sometimes nominate the intercostobrachial nerve (ICBN) as a landmark of the superior extent of an axillary sample. A more formally worded description runs:

‘The removal of tissue from below the axillary vein superiorly and the lateral border of pectoralis minor medially. This differs from a formal level I clearance in that the lateral aspect of the axilla and the subcapsular fossa are not dissected. The nerves to latissimus dorsi and serratus are not identified.’59

Given the differing appreciation of what an axillary sample involves, the number of lymph nodes harvested from such procedures varies. Kissin demonstrated a 24% error rate when sampling was compared with complete axillary clearance.66 In Forrest’s initial reports, sampling failed to retrieve any lymph nodes in 18% of cases although the success rate improved substantially later.67 It is thus difficult to interpret and compare the results of axillary sampling procedures in breast cancer. However, the technique remains an accepted axillary approach in many international centres.
Appendix II

Risks of axillary dissection and irradiation

Risks of axillary dissection

Seroma

Seromas are common following most types of axillary clearance, but are reported to be less with axillary sampling. The ideal period of drainage is unknown and the management of drain tubes and of seromas is very individualised. Randomised trials have shown little difference in seroma formation, regardless of the drainage technique employed. Even with prolonged periods of drainage, some patients still require further aspiration of residual seroma.

Wound infection

The rate of wound infection in axillary surgery has been reported at approximately 10%. Wound infection is more common in certain groups of patients: the elderly and immuno-compromised; those who undergo repeated aspiration of seroma or prolonged wound drainage; and those who have undergone recent surgery in the vicinity of the axilla.

The prophylactic use of antibiotics has been shown to decrease the rate of wound infection.

Reduced shoulder mobility and stiffness

Shoulder stiffness is common immediately after axillary dissection. Patients may be predisposed to this if they have pre-existing arthritis, or if the position of the arm during the surgery is not carefully monitored. Early mobilisation and exercise is important for retaining normal mobility post-operatively. There is little documented evidence on the cause of this problem.
**Damage to motor nerves**

Although the frequency of injury appears to be low, three important motor nerves are at risk during axillary lymph node dissection:

- The medial pectoral nerve is at risk when dissecting around pectoralis minor. This is particularly so if this muscle is divided, but the nerve may also be damaged during dissection as it swings along the lateral border of the pectoralis minor muscle. In up to one-third of patients, it lies well lateral to the muscle and is at significant risk. Damage to the nerve results in minimal morbidity, but will lead to wasting of the lower fibres of pectoralis major. This will result in the loss of the anterior axillary fold, and perhaps a less than desirable cosmetic result.

- The long thoracic nerve of Bell or nerve to serratus anterior runs along the chest wall in the posterior part of the axilla. Damage to this nerve results in winging of the scapula.

- The thoracodorsal nerve or nerve to latissimus dorsi may be divided in the lateral aspect of the axilla. Although damage to this nerve may result in minimal detectable disability, some reduction in the power may be noticed, especially when the arm is raised above the head and in women active in sports.

**Numbness and paraesthesia**

Various studies have looked at this common problem and estimated that some numbness may be demonstrated in almost 80% of patients undergoing axillary surgery. The frequency of more significant or disabling pain is in the range of 5%. The alteration to sensory perception is assumed to result from division of the ICBN.

The extent of any deficit is variable but may involve the inner aspect of the upper arm, shoulder, axilla and anterolateral chest wall.
Although many surgeons preserve the ICBN, this is not necessarily reflected in the preservation of normal sensation. Some units have demonstrated a better outcome with ICBN preservation at 12 months; however, a recent report from France failed to observe any difference regardless of whether the nerve was divided. Importantly, preservation of the ICBN is not affected by the extent of axillary clearance.

**Lymphoedema**

Lymphoedema is one of the most significant side effects of intervention to the axilla with either radiotherapy and/or surgery. Research into lymphoedema is made difficult by the varying definitions used and by the significant differences between the subjective and objective appreciation of the problem. Various studies have reported the incidence of lymphoedema to run between 10–25%. The incidence of ‘clinically obvious’ lymphoedema associated with axillary clearance is approximately 7%. However, the incidence of lymphoedema varies widely depending upon the point post-treatment at which it is assessed. Some studies suggest that its incidence increases with time following surgery, and certainly it remains a difficult treatment problem. Patient size may be the best predictor of lymphoedema risk, with those with a high body mass index (BMI) being at higher risk. Other factors which may contribute to risk are hypertension, disruption of sympathetic nervous input to the limb and anatomical situations where few primary lymphatic channels exist.

**Risks of axillary irradiation**

**Lymphoedema**

The routine addition of radiotherapy to a fully dissected axilla increases the incidence of lymphoedema to at least 30%. Management of the axilla with radiation alone is reported to induce lymphoedema of the arm in rates similar to that of surgery alone (3–8%).

Radiation therapy to a conserved breast may include some level I of the axilla. There is randomised trial evidence that the risk of lymphoedema is not increased in this situation.
**Shoulder and arm movement restriction**

This is relatively common (approximately 20%), even when the shoulder joint is routinely excluded from the radiation beam.\(^{12}\) It may be due to the effects of radiation on the pectoral and other muscles associated with shoulder movement.

**Rib fracture**

This is mostly due to the chest wall or breast fields. The risk of rib fracture in those areas, based on several large reviews, is 1.8%.\(^{2,75}\) The risk of such fractures in the axillary field areas is much less.

**Brachial plexus damage**

This can occur in breast cancer due to the effects of radiation, or due to tumour recurrence in the brachial plexus or supraclavicular fossa. The major factors responsible for radiation-induced plexopathy are a total radiation dose exceeding 50 Gray (Gy); high dose per fraction treatment; techniques delivering the dose through a single anterior field; using orthovoltage radiation; and concurrent chemotherapy. The risks range from 0–1.8%.\(^{75,76,77}\) The use of techniques that may lead to field junction overlap increase the risk of this problem.

**Pneumonitis**

This complication occurs in up to 7% of patients.\(^{75}\) It is seen more commonly where the volume irradiated is large, as when the supraclavicular fossa and axilla are included in the field. The risk is as low as 0.5% for radiation therapy alone to the breast or chest wall alone. This risk increases with the addition of supraclavicular fossa and axillary radiation fields and with the addition of chemotherapy.\(^{75}\)

**Sarcomas**

The development of radiation-induced sarcomas is rare. They occur in bone or soft tissue and most have involved orthovoltage therapy. A review of the evidence in 1995 suggested an incidence of 1–2 per 1,000 treated patients who are alive at 10 years.\(^{78,79}\)
Appendix III

Sentinel node biopsy in breast cancer

The concept of sentinel node biopsy was first described by Cabanes in the management of penile cancer. Previous to this it was assumed that drainage of a primary tumour to the draining lymph nodes was a random phenomenon. Morton et al. demonstrated that for cutaneous melanoma the first node that drained the site of the primary lesion (i.e., the sentinel node) could be reliably identified. They further demonstrated that the spread of disease within the draining node basin followed in sequence from sentinel node to higher echelon nodes; and that biopsy of the sentinel node could be used to stage the nodal basin. Specifically, if the sentinel node did not contain any tumour then the likelihood that any other nodes in that nodal basin would be involved was extremely small.

The technique of sentinel node biopsy has been generalised from cutaneous melanoma to a number of malignancies, including breast cancer, and a number of groups have reported their experience. Three techniques usually in combination have been used to identify the sentinel node/s in women with breast cancer. Guilano et al. use only peritumoral injection with a vital dye (Patent Blue V in Australia) to identify the sentinel node, which stains blue. This technique has the lowest success rate although more recent results are much improved. Most groups employ the technique of peritumoral injection with a radioactive labelled colloid particle pre-operatively, and intra-operative use of a hand-held gamma probe to identify the sentinel node taken up by the radio labelled colloid. Many of these groups have also combined this technique with lymphoscintigraphy, which involves imaging the woman after injection with the radio labelled colloid to visualise spread among the lymphatics to the first or sentinel node. This technique not only provides a guide as to the site of the sentinel node (which in a small number of cases may not be the axilla) but also indicates if there is more than one sentinel node. Uren et al. in a small series described lymphatic drainage in patients with carcinoma of the breast. The ipsilateral axilla was involved in 85% of cases but in nearly one-third of cases there was cross breast spread to axilla or internal mammary nodes. Unexpectedly and potentially of considerable interest, 20% of patients had spread to chest wall or clavicular nodes.
The most favoured technique – and that which is associated with the best result – employs pre-operative lymphoscintigraphy and intra-operative use of hand-held gamma probe after injection of a radio-colloid and use of the vital blue dye. The optimal technique is still under evaluation. Such factors as the site of the injection of the radio-colloid or blue dye have not yet been resolved. Most groups have injected dye and colloid peri-tumourally, although there is some evidence that subcutaneous injection in the skin over the tumour may be as accurate and clearly has advantages for women with impalpable lesions.\textsuperscript{51} Regardless of the experience of the operator, successful identification of the sentinel node appears to be less in the elderly and in patients who have undergone a previous excision of the primary tumour. At this time, it is therefore not possible to make any firm recommendations about the optimal technique.

On the other hand, there is clear and emerging evidence of a considerable learning curve for successful performance of this procedure.

There is no doubt that sentinel node biopsy in the reported series\textsuperscript{49,50,51} is highly accurate in predicting the status of the axillary nodal basin, but as yet there is no information concerning the small proportion of patients in whom the sentinel node is not in the axilla. As has occurred with melanoma, the use of multiple histological sections through the sentinel node and of immunohistochemistry to facilitate the identification of micro-metastases is likely to increase the rate of node involvement.\textsuperscript{84} The significance of these micro-metastases in patients with small and otherwise good prognosis tumours is unknown, although previous studies suggest that micro-metastases are probably associated with poorer long term survival.\textsuperscript{85} Whether this can be impacted by current systemic therapies is not yet known.

In summary, the current data indicate that sentinel node biopsy is a highly effective and accurate method of staging the axilla with little surgical morbidity. The technical difficulty and the considerable learning curve of the procedure cannot be underestimated. There are significant differences in accuracy reported in one series that examined experienced versus inexperienced operators.\textsuperscript{52} Considerable concerns remain about the optimal technique; the long-term safety of avoiding axillary dissection in patients with good prognosis lesions; and the clinical
significance of micro-metastases and what should be done about them. Clinical trials are currently under way to address these issues. At present, sentinel node biopsy without complete axillary lymphadenectomy cannot be recommended as standard management.
Appendix IV

Technical aspects of radiation therapy to the axilla

The axilla will not routinely be treated in isolation from the supraclavicular fossa. The depth required to treat in the supraclavicular area should be considered. The depth in the axilla must also be determined, and generally the dose should be taken sufficiently posteriorly to include the posterior axillary area fully.

Radiation therapy for both areas is generally performed using unmatched anterior and posterior portals. Generally, the supraclavicular portal will be irradiated from the anterior surface only, and the axilla from the anterior and posterior surface. The area of the axillary apex or the coracoid process is generally chosen to determine the medial edge of the posterior field. If the axilla is to be excluded from the treatment volume, the coracoid process forms the most lateral extent of the field.

It may be desirable to angle the anterior portal away from the spinal cord. If a direct portal is used, it is recommended to calculate dose to the spinal cord.

The potential for overlapping fields to produce areas of overdose or underdose at the junctions should be addressed. Methods to minimise these include:

1. Using isocentric techniques to allow the use of asymmetric jaws on all fields so that central axis rays are aligned at the junction. Half beam blocking may also be used.
2. Using a calculated gap in the junction area to limit the dose to an acceptable limit.
3. Avoiding turning the patient prone to deliver the posterior axillary boost.

Supervoltage equipment (4, 6 or 8 MV or Cobalt-60) are preferred because of dose homogeneity and skin sparing.
The aim is to create a homogenous dose distribution throughout the treatment volume (+5% variation). Factors to achieve this in axillary treatment include:

1. Choice of beam energy.
2. Lung correction should be used wherever possible.
3. Contours through the nodal areas should be given.
4. Dose should be recorded as per ICRU 50.

The prescribed dose is given in 1.8–2.25 Gy fractions at the rate of 9 or 10 times per fortnight. In general, a dose of 45–52.5 Gy is prescribed. All fields should be treated each day, although the posterior axillary boost is typically given in fewer fractions.

Careful attention to the amount of lung included within the treatment volume will decrease the risk of pneumonitis.
References


References


53 Macmillan RD, Barbera D, Hadjiminas DJ, et al. Prospective comparison study of sentinel node biopsy and four-node sampling to stage the axilla. Abstract. 6th Nottingham International Breast Cancer Conference, September 1999, Nottingham, UK.


