

## Special Supplement

See page S83 for a list of the members of the Steering Committee

See page S25 for the names of those who also contributed to the authorship of this document

This guideline has been peer reviewed.

# 4. Axillary dissection

## The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer

### Abstract

**Objective:** To provide information needed by patients with breast cancer (stages I and II) and their physicians when deciding whether axillary dissection should be carried out.

**Options:** No axillary surgery; removal of all axillary lymph nodes; removal of level 1 and 2 nodes; axillary "sampling."

**Outcomes:** Accurate determination of stage of cancer, resulting in better-informed therapeutic decisions; reduction of recurrence in axillary lymph nodes; improved survival.

**Evidence:** A systematic review of English language literature based on MEDLINE and CANCERLIT databases to September 1996, with nonsystematic review continued to June 1997. The nature of the evidence or opinion is classified as shown on page S2.

**Benefits:** Optimal therapy, with maximal survival and minimal local recurrence.

**Harms:** Increased postsurgical morbidity.

### Recommendations:

- Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early, invasive breast cancer.
- For accurate staging and to reduce the risk of recurrence in the axilla, level 1 and level 2 nodes should be removed.
- Patients should be made fully aware of the frequency and severity of the potential complications of axillary dissection.
- Irradiation of the axilla should be carried out with caution after axillary dissection.
- Omission of axillary dissection may be considered when the risk of axillary metastasis is very low or when knowledge of node status will have no influence on therapy.
- Patients should be offered the opportunity to participate in clinical trials whenever possible.

**Validation:** Initial draft guidelines were successively reviewed and revised by a writing committee, expert primary reviewers, secondary reviewers chosen from all regions of Canada and by the Steering Committee. The final document reflects a consensus of all these contributors.

**Sponsor:** The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer was convened by Health Canada.

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The question of whether, and to what extent, axillary lymph nodes should be removed at the time of surgery for breast cancer does not yet have a clear-cut answer. On the one hand, surgical removal of these nodes provides important information for determining the stage of the cancer and, in addition, reduces the rate of recurrence of axillary cancer. Unfortunately, however, axillary dissection may be associated with significant long-term morbidity. Thus, the decision on whether to remove axillary nodes and how extensively to do so requires a balancing of the expected health gains versus side effects.

These guidelines attempt to synthesize the available information with the objective of helping patients and their physicians make these decisions. The evidence is gathered from randomized controlled studies or cohort studies and, when such evidence is not available, expert opinion is used. The evidence is classified into 5 levels (see page S2).

## Method

MEDLINE (1980 to September 1996) and CANCERLIT (1983 to September 1996) databases were systematically searched for relevant references using the following key words: breast cancer, axillary nodes, axillary dissection, axillary recurrence. Nonsystematic review of the breast cancer literature was continued to June 1997. Two draft guidelines prepared by the authors were integrated by a writing committee consisting of 5 members

of the Steering Committee. The document then underwent successive reviews, first by 4 expert primary reviewers and then by all members of the Steering Committee. The prefinal draft was then submitted to secondary reviewers consisting of surgical, radiologic and medical oncologists, breast cancer survivors, nurses and family physicians chosen from across Canada. All changes were reviewed by the authors of the initial drafts. The final revised document was approved by the Steering Committee and represents a consensus of all contributors.

## Recommendations

- **Removal and pathological examination of axillary lymph nodes should be standard procedure for patients with early, invasive breast cancer.**
- **For accurate staging and to reduce the risk of recurrence in the axilla, level 1 and level 2 nodes should be removed.**

Removal and pathological examination of the axillary lymph nodes has long been standard treatment for patients having operable breast cancer. Its continued utilization has been advocated by the United States National Institutes of Health Consensus Conference on Early Breast Cancer,<sup>1</sup> the Australian First National Breast Cancer Consensus Conference,<sup>2</sup> and 2 Canadian provinces that have published guidelines for the treatment of cancer<sup>3,4</sup> (level IV evidence). The principal reason for this substantial consensus in favour of axillary dissection is that it provides accurate staging and prognostic information, which helps guide the selection of systemic adjuvant therapy. In addition, it results in lower rates of axillary regional metastasis.

### Axillary dissection and staging

The presence or absence of metastatic involvement of the axillary lymph nodes is the most powerful prognostic factor available for patients with primary invasive breast cancer.<sup>5</sup>

In 2 substantial follow-up series of patients with breast cancer, a clear relationship has been shown to exist between survival and the absence or presence (and number of) involved axillary lymph nodes (level III evidence).<sup>6,7</sup> Unfortunately, node involvement can not be estimated accurately by clinical examination alone.

The only method of determining axillary lymph-node status with accuracy is surgical removal and histologic examination of nodes (level III evidence).

Clinical examination of the axilla is inherently inaccurate. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study, 27% of patients thought to have axillary metastases on clinical grounds had, in fact, no such involvement. At the same time, 39% of patients thought to be without axillary involvement actually had metastases (level III evidence).<sup>8</sup> Since knowledge of the presence and extent of nodal involvement is important for the selection of appropriate adjuvant therapy (see guidelines 7 and 8), this means that axillary dissection must be considered.

Although there is consensus regarding the need for surgical removal of axillary lymph nodes for the purpose of staging, there is less agreement concerning the number of nodes to be removed. In the B-04 study it was concluded that the qualitative nodal status (node-positive or node-negative) can be accurately determined when only 3 to 5 nodes are removed. However, the quantitative nodal status, involvement of 1 to 3 nodes or more, is more reliably estimated on the basis of dissection of 10 nodes (level III evidence).<sup>8</sup> This conclusion is supported by a study involving mathematical modelling of the outcomes of 1446 axillary dissections and the findings of the Danish Breast Cancer Cooperative Group.<sup>9,10</sup>

The axillary lymph nodes are located at 3 levels as defined by their relationship with the pectoralis minor muscle.<sup>11,12</sup> Level 1 nodes are those situated lateral to or below the lateral border of the pectoralis minor muscle. These nodes receive most of the lymphatic drainage from the breast. Level 2 nodes are situated deep to the pectoralis minor muscle and receive lymph from level 1 nodes and also some drainage directly from the breast. Level 3 nodes lie medial to the pectoralis minor muscle in the infraclavicular fossa. They receive drainage from the previous 2 levels of nodes but may also receive some lymph directly from the superior part of the breast.

When cancer develops in the breast, the axillary nodes are usually involved sequentially: first those in level 1, then level 2 and lastly level 3. However, isolated involvement of level 2 and/or level 3 nodes can occur ("skip involvement"). Level 3 nodal involvement alone is rare, occurring in less than 3% of patients. In one study, level 2 nodes were involved but not level 1 nodes in up to 25% of patients in whom this feature was examined.<sup>13</sup> In contrast, in the Milan study of 539 patients with carcinoma of the breast who underwent total axillary dissection, level 1 nodes only were involved in 58%, both levels 1 and 2 nodes in 22%, all 3 levels in 16% and skipping distribution in only 4%.<sup>14</sup> Thus, because the nodes in levels 1 and 2 are frequently involved, it is current practice to remove all nodes found in these 2 levels. This practice seldom gives rise to significant lymphedema and is recommended by the 2 consensus conferences and 2 guidelines previously mentioned (level IV evidence).<sup>1-4,15</sup> The removal of level 3 nodes involves greater morbidity and seldom adds useful information.<sup>16</sup>

Levels 1 and 2 dissection usually results in the removal of 10 or more nodes, which is sufficient to determine the stage of breast cancer correctly in approximately 97% of patients.<sup>12,17</sup> However, dissection that is limited to level 1 may result in the incorrect staging of as many as 25% of patients (level III evidence).<sup>12</sup> Thus, consistent removal of fewer than 10 nodes should lead to a review of surgical and pathological techniques (level V evidence).

New techniques of lymphatic mapping are promising. These involve the use of markers such as vital blue dye and technetium-labelled sulfur colloid to identify a sentinel node that drains lymph from the tumour area.<sup>18,19</sup> For example, in a study of 62 patients, the sentinel node was identified successfully in 92% of cases and was positive in all patients found to have metastatic disease. There were no skip metastases.<sup>20</sup> If such results are confirmed, a considerable amount of axillary

dissection and upper limb morbidity may be avoided in the future.

### ***Axillary dissection and local recurrence***

#### **Removal of axillary lymph nodes also reduces the risk of recurrence of cancer in the axilla.**

In the absence of axillary dissection, recurrence of cancer in the axilla after breast surgery is common. A retrospective review of patients who underwent lumpectomy without axillary dissection showed a 10-year average recurrence rate of 28% in the axilla. This recurrence rate varied with tumour size, averaging 10% when the primary tumours were 1 cm or less in diameter, 26% when the primaries were 1.1 to 2.0 cm in diameter and 33% when the primaries were 2.1 cm or greater in diameter (level III evidence).<sup>21</sup>

In the NSABP trial B-04, mastectomy without axillary surgery was associated with an axillary recurrence rate of 17.8% in clinically node-negative cases. In contrast, radical mastectomy, which includes axillary dissection, was associated with axillary recurrence rates of 3.1% for node-positive patients and 1.0% for node-negative patients (level I evidence).<sup>22</sup>

Retrospective follow-up studies of substantial case series involving breast-conserving surgery and axillary dissection have shown axillary recurrence rates of 0.3% in node-negative patients<sup>23</sup> and 2.1% in patients who had fewer than 4 involved nodes<sup>24</sup> (level III evidence).

#### **The risk of recurrence in the axilla is inversely related to the number of lymph nodes removed (level III evidence).**

Several studies have demonstrated that thorough dissection is associated with a greater reduction in the risk of recurrence than sampling of a few nodes. In a study of 3128 clinically node-negative patients, the 5-year probability of recurrent cancer in the axillary lymph nodes ranged from 19% when no nodes were removed to 3% when more than 5 nodes were removed.<sup>25</sup> Comparable results are reported by others.<sup>8,26</sup> In the B-04 study, no patient who had 6 or more nodes removed had a recurrence in the axilla.<sup>22</sup> Thus, more than minimal sampling is necessary to reduce recurrence rates and achieve adequate staging (level III evidence).

### ***Axillary dissection and survival***

It has been suggested that axillary dissection may result in improved survival.<sup>27</sup> However, the evidence suggests that if such an effect does exist, it is small.

In the NSABP B-04 trial, women under 70 years of age with early breast cancer and clinically negative axillary nodes were randomized to receive 3 different forms of treatment, 2 of which were radical mastectomy, which includes complete axillary dissection, and total mastectomy, which does not.<sup>22</sup> The overall survival at 10 years was 58% for those who underwent radical mastectomy and 54% for those who under-

went total mastectomy, a difference that is not statistically significant (level II evidence).

Other evidence suggesting the possibility of improved survival from axillary dissection comes from a trial in which 658 women under 70 years of age with early breast cancer were randomized to undergo either lumpectomy with breast and axillary radiation (but no axillary dissection) or lumpectomy with axillary dissection plus breast irradiation.<sup>28</sup> There was a small but significantly greater overall 5-year survival ( $p = 0.014$ ) in the women who had axillary dissection (96.6%) compared to those who did not (92.6%) (level I evidence). However, it is possible that this apparent benefit was because 11 patients in the axillary dissection group received adjuvant chemotherapy, whereas those in the other group did not.

Other suggestive evidence can be seen in a follow-up series of 3128 consecutive patients with breast cancer in whom axillary "sampling" of fewer than 5 lymph nodes resulted in increased recurrence in the axilla and worse 5-year survival than those patients who received more extensive axillary surgery (level III evidence).<sup>25</sup>

An extensive review of the evidence published up to 1995 concluded that the available data suggest, but do not prove, that the initial use of axillary treatment, either by surgery or radiotherapy, may result in a small improvement in long-term outcome in some patient subgroups (level III evidence).<sup>29</sup>

### ***Axillary dissection and surgical morbidity***

- **Patients should be made fully aware of the frequency and severity of the potential complications of axillary dissection.**

Axillary dissection can be accompanied by both short- and long-term complications, their frequency and severity varying with the extent of axillary surgery undertaken.<sup>29</sup> The arm problems that occur after breast surgery (stiffness, loss of sensation, swelling) are more frequent when the axilla is also dissected. In a follow-up study at 18 months, the mean number of arm problems experienced by women who had axillary dissection was 2.5 per patient compared with 0.9 per patient in women who did not undergo axillary dissection ( $p = 0.0001$ ) (level III evidence).<sup>30</sup>

Postoperative infection (breast and axilla) is reported to occur in 5% to 14% of patients. It occurs more frequently in elderly or poorly nourished women, when there has been prolonged catheter drainage, or after recent breast surgery such as surgical biopsy or repeated percutaneous seroma aspiration (level III evidence).<sup>31,32</sup> Prophylactic use of antibiotics has been shown to decrease the rate of wound infection (level I evidence).<sup>33</sup>

The intercostobrachial nerve can be inadvertently damaged during axillary dissection, causing numbness and dysesthesia in the inner side of the upper arm. One review has estimated the frequency of significant and sometimes disabling pain to be 4% to 6%. In a study carried out 1 year after surgery, numbness in the intercostobrachial nerve distribution was found in almost 80% of patients.<sup>34</sup>

Some restriction of shoulder movement is not uncommon, occurring in 17% of women in the study mentioned above (level III evidence).<sup>34</sup> However, the "frozen shoulder" of previous eras is said to be virtually never seen now.<sup>17</sup>

Lymphedema is one of the most dreaded complications of axillary dissection and, once established, is refractory to treatment. Its frequency varies with the extent of the operation.<sup>35-37</sup> The reported frequency also varies with the definition of lymphedema that is used. When definitions are based on both subjective and objective criteria, frequencies of 11% to 27% are reported.<sup>34,36,38,39</sup> However, when described as "clinically obvious," lymphedema is reported to occur in 2% to 7% of patients.<sup>36,40,41</sup> In one series, objectively observed but not severe swelling occurred in 10% of women after "complete axillary dissection" (level III evidence).<sup>42</sup>

- **Irradiation of the axilla should be carried out with caution after axillary dissection.**

Irradiation of the axilla alone can cause lymphedema, and when done after axillary dissection it may cause increased morbidity, particularly when the dissection has been extensive.<sup>17,36</sup> In one study, the 6-year actuarial risk of symptomatic lymphedema developing was 4% after radiotherapy alone, 6% after level 1 or 2 dissection with radiotherapy, and 36% after complete level 1, 2 and 3 dissection with radiotherapy (level III evidence).<sup>43</sup> Therefore, it is recommended that when axillary dissection has been carried out, radiotherapy should be considered only when the risk of recurrence is increased.<sup>3</sup>

### **Should axillary dissection ever be omitted?**

- **Omission of axillary dissection may be considered when the risk of axillary metastasis is very low or when knowledge of node status will have no influence on therapy.**

In view of the morbidity associated with axillary dissection, it would theoretically be desirable to omit this procedure whenever the possible morbidity clearly outweighed the clinical benefits. However, it is uncertain whether this strategy is ever justified.<sup>44,45</sup>

In ductal carcinoma in situ (DCIS) in the absence of invasion, axillary metastasis occurs in less than 1% of patients. Accordingly, there is considerable agreement that axillary dissection is not warranted in patients with DCIS.

Apart from DCIS, low rates of recurrence in the axilla are associated with small tumour size, low nuclear grade, estrogen receptor positivity and postmenopausal status.<sup>5</sup> It has been shown that mammographically detected lesions less than 5 mm in diameter are associated with a rate of axillary metastasis of 5% or less.<sup>29</sup> However, significant axillary lymph-node involvement can still occur in the presence of these factors. In the presence of invasive cancer, there is insufficient evidence for omitting axillary dissection at present.

It has been suggested that some frail, elderly patients with a clinically negative axilla might be spared axillary dissection because it will seldom influence the decision of whether to

use adjuvant systemic therapy (level IV evidence).<sup>46,47</sup> An example of this situation is an older woman with breast cancer who will be given tamoxifen but not chemotherapy, even if positive axillary nodes are found.

### **Clinical trials**

- **Patients should be offered the opportunity to participate in clinical trials whenever possible.**

As has been frequently noted, the knowledge base for many of the therapeutic interventions involved in the treatment of breast cancer often does not exist or is extremely weak. These particular areas of uncertainty, where guidelines must, at present, be based on level III, IV, or V evidence, can only be eliminated by well-designed, randomized, controlled trials. Improvement in the care of future patients with breast cancer is thus dependent on the participation of sufficient numbers of patients in such trials. Physicians treating patients with breast cancer should therefore be aware of currently available trials and should offer their patients the option of participation.

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