Clinical practice guidelines for the care and treatment of breast cancer: 3. Mastectomy or lumpectomy? The choice of operation for clinical stages I and II breast cancer (2002 update)

Hugh Scarth, Jacques Cantin, Mark Levine, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer*

Dr. Scarth is Assistant Professor in the Department of Surgery, Dalhousie University, and is with the Atlantic Health Sciences Corporation, Saint John, NB. Dr. Cantin is Associate Professor in the Department of Surgery, University of Montreal, and is with the Centre hospitalier de l'Université de Montréal, Montreal, Que. Dr. Levine is Professor in the Departments of Clinical Epidemiology and Biostatistics and of Medicine and is the Buffet Taylor Chair in Breast Cancer Research, McMaster University, Hamilton, Ont.

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Abstract

Objective: To assist women and their physicians in making the most clinically effective and personally acceptable decision regarding the choice of primary surgery for potentially curable breast cancer.
Options: Breast-conserving surgery (BCS; also referred to as lumpectomy or wide local excision) or mastectomy.
Outcomes: Local recurrence, disease-free survival, overall survival, cosmetic results.
Evidence: Systematic computerized search of MEDLINE (1980 to May 2001) and CANCERLIT (1985 to May 2001). Nonsystematic review of breast cancer literature to December 2001.
Benefits: Minimization of disfigurement offered by BCS.
Harms: The need for radiotherapy and the greater costs associated with BCS.
Recommendations:

- For patients with stage I or II breast cancer, BCS followed by radiotherapy is generally recommended. In the absence of special reasons for selecting mastectomy, the choice between BCS and mastectomy can be made according to the patient's circumstances and personal preferences.

- Mastectomy should be considered in the presence of any of the following:
    a. factors that increase the risk of local recurrence such as extensive malignant-type calcifications visible on the mammogram, multiple primary tumours or failure to obtain tumour-free margins;
    b. physical disabilities that preclude lying flat or abducting the arm, thus preventing the use of radiotherapy;
    c. absolute contraindications for radiotherapy such as pregnancy in the first or second trimester or previous irradiation of the breast, or relative contraindications such as systemic lupus erythematosus or scleroderma;
    d. large tumour size in proportion to breast size;
    e. the patient's clear preference for mastectomy.
- The following factors are not contraindications for BCS: the presence of a centrally located tumour mass, axillary lymph-node involvement or the presence of breast implants.
- In some cases, preoperative chemotherapy can shrink a large primary tumour and allow for BCS.
- Before deciding between BCS and mastectomy, the physician must make a full and balanced presentation to the patient concerning the pros and cons of these procedures.
- Whenever an open biopsy is performed on the basis of even modest suspicion of carcinoma, the procedure should be, in effect, a lumpectomy, using wide local excision of the intact tumour surrounded by a cuff of tumour-free tissue (determined by palpation and visual inspection).
- The following recommendations should be observed to provide optimum clinical and cosmetic results:
    a. tumour-involved margins should be revised;
    b. separate incisions should be used for removal of the primary tumour and for the axillary dissection except when these coincide anatomically;
    c. curvilinear incisions, concentric with the areolar margin, or transverse incisions are recommended over radial incisions.
    d. drains and approximation sutures should not be used in the breast parenchyma.

Validation: The authors' original text was revised by a writing committee, primary and secondary reviewers, and by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The final document [1998] reflected a consensus of all these contributors. A writing committee updated the original guideline and then submitted it for further review, revision and approval by the steering committee. The current update did not undergo external review.

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Until the mid-1980s the treatment for stage I or II breast cancer was removal of the breast by total mastectomy together with removal of the axillary lymph nodes. Since then, the evidence from 6 prospective randomized trials has shown that removal of only the tumour, leaving most of the breast intact, results in the same survival as mastectomy.

Breast-conserving surgery (BCS) refers to removal of the tumour along with a cuff of normal tissue while preserving the cosmetic appearance of the breast. BCS is also referred to as lumpectomy or wide local excision. Mastectomy refers to removal of the entire breast, including the nipple and areola complex and the fascia over the pectoralis muscles while sparing the underlying muscles and innervation. Axillary lymph node dissection is usually carried out with BCS or mastectomy. (This issue is considered in **guideline 4**.)

Apart from certain exceptions (discussed further on), the choice between breast-conserving procedures and mastectomy for stages I and II tumours depends on individual circumstances and personal preference. Considerable evidence that has now accumulated regarding survival and local recurrence rates related to both procedures is summarized in this guideline to help patients and their physicians make the most clinically effective and personally acceptable decisions regarding the extent of primary surgery.

Methods

This guideline document is based on a systematic review of the English-language literature retrieved from MEDLINE (1980 to May 2001) and CANCERLIT (1985 to May 2001). The key terms used for the search were "breast neoplasms," "mastectomy, segmental," "lumpectomy" and "breast conservation." The search was restricted to randomized controlled trials, meta-analyses and review articles. References from review articles and textbook chapters were also reviewed. A nonsystematic review of the breast cancer literature was continued to December 2001. The quality of the evidence on which conclusions were based is categorized into 5 levels. The iterative process used to develop this guideline is described previously.[1] A writing committee updated the original guideline and submitted it for further review, revision and approval by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer.

Recommendations (including evidence and rationale)

Mastectomy versus breast-conserving surgery and radiotherapy

Before considering which procedure to recommend, the nature and extent of the tumour must be established precisely using clinical and mammographic

information (see **guidelines 1 and 2**). Once the diagnosis of clinical stage I or II breast cancer is established, the choice of surgery can be made based on the information outlined below.

- **For patients with stage I or II breast cancer, BCS followed by radiotherapy is generally recommended. In the absence of special reasons for selecting mastectomy, the choice between BCS and mastectomy can be made according to the patient's circumstances and personal preferences.**

Six prospective, randomized, controlled trials have shown that, in patients with operable breast cancer, the outcome after BCS with radiotherapy is equivalent to that after mastectomy with respect to distant recurrences and overall survival (level I evidence).[2–10] The results of these trials are summarized in Table 1.[2,3,5,6,8,9] The trial with the highest statistical power is the multicentre National Surgical Adjuvant Breast Project (NSABP) protocol B-06, which compared BCS with and without radiotherapy to mastectomy in 1843 women with stage I or II tumours in whom BCS was cosmetically feasible.[4,5,10] After an average of 12 years of follow-up, disease-free survival and overall survival were still identical among patients treated by BCS with or without radiotherapy and among those treated by mastectomy, although local recurrence was much more frequent when radiotherapy was omitted after BCS (see **guideline 6**).[4,5,10] The results of the NSABP B-06 trial came under scrutiny in 1993, after allegations that some fraudulent data had been provided by a study centre. However, when the results were re-analyzed without that centre's data, the conclusion regarding the equivalence of the surgical procedures was unchanged.[5,11]

Since BCS with radiotherapy results in equivalent survival to mastectomy, the choice between them can be exercised on other grounds. The advantage of BCS is that it conserves the breast. The disadvantage is the need for radiotherapy, which in addition to being time-consuming may also be logistically difficult and costly if the patient lives far from the treatment facility. Radiotherapy may also cause adverse effects such as swelling, pain, skin pigmentation and fibrosis of the breast (see guideline 6).[12,13]

According to the studies outlined in Table 1,[2,3,5,6,8,9] after radiotherapy, local recurrence or a second cancer in the same breast may affect 3.3% to 20% of women over the next 15 years depending on the extent of surgery, the patient's age and the characteristics of the tumour. The majority of patients in the study reported by van Dongen and coauthors[6] had stage II disease. The risk of local recurrence or a second cancer is comparable to the risk of recurrence in the chest wall after mastectomy alone (2.3%–14%) (Table 1). However, with increasing use of chemotherapy, current recurrence rates are lower than this: in NSABP protocol B-13 the local recurrence rate dropped from 13% to 2.6% with the use of sequential methotrexate and 5-fluorouracil; in protocol B-19 it was 0.6% with the use of cyclophosphamide–methotrexate–fluorouracil therapy.[14] For women with estrogen receptor-positive tumours, tamoxifen produced equivalent changes in local recurrence rates.[15] Thus, with the increasingly routine use of systemic

adjuvant therapies, lumpectomy and radiation therapy provide very adequate long-term local control.

Recurrence of breast cancer necessitates a second and wider excision or even a mastectomy, which can be psychologically distressing and, for some, devastating. To help prevent this possibility one must weigh the impact of an immediate mastectomy, which can also be distressing.

A National Institutes of Health Consensus Conference, which evaluated the information on BCS, stated that lumpectomy was the preferred treatment because it provided equivalent survival and preserved the breast.[16] Thus, the choice usually can be based on personal preference. However, under certain conditions, as follows, mastectomy is recommended.

Special reasons for selecting mastectomy

- **Mastectomy should be considered in the presence of any of the following:**

a. **factors that increase the risk of local recurrence such as extensive malignant-type calcifications visible on the mammogram, multiple primary tumours or failure to obtain tumour-free margins;**

b. **physical disabilities that preclude lying flat or abducting the arm, thus preventing the use of radiotherapy;**

c. **absolute contraindications for radiotherapy such as pregnancy in the first or second trimester or previous irradiation of the breast, or relative contraindications such as systemic lupus erythematosus or scleroderma;**

d. **large tumour size in proportion to breast size;**

e. **the patient's clear preference for mastectomy.**

<u>Increased risk of local recurrence</u>

Mastectomy is usually necessary when the mammogram shows widespread clusters of malignant-type calcifications throughout the breast,[15] when there are multiple primary tumours[17] or when clear (tumour-free) margins in excised tissue are not obtained, even after surgical revision of the original excision.

A number of case series have examined whether microscopically positive margins are associated with increased rates of recurrence in the breast.[18–22] Some studies have reported no increase in recurrence rates when margins were focally involved

with tumour,[18] whereas others have reported an increase in rates of local breast cancer recurrence when surgical margins were positive (level IV evidence).[19] The best evidence supporting the view that positive margins predict local breast recurrence comes from 2 randomized trials. In the Milan II trial, over 700 women were randomly assigned to undergo quadrantectomy plus axillary dissection and breast irradiation or lumpectomy plus axillary dissection.[23] In the 178 quadrantectomy patients in whom margins were assessed, there was 1 local recurrence (12.5%) in the 8 patients with positive margins, compared with 6 (3.5%) in the 170 patients with negative margins. The corresponding rates among the 289 lumpectomy patients in whom margins were assessed were 17.4% and 8.6% (level II evidence). In the trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), women with breast cancer were randomly assigned to undergo modified radical mastectomy or lumpectomy plus axillary dissection and breast irradiation.[24] In the lumpectomy group, 31 (14%) of 218 women with positive margins had breast cancer recurrence, compared with 17 (8%) of 213 with negative margins ($p < 0.05$) (level I evidence). Finally, data from 2 NSABP randomized trials involving women with ductal carcinoma in situ who had lumpectomy provide supporting evidence that even margins with noninvasive breast cancer are associated with an increased risk of local recurrence. In the NSABP B-17 trial breast irradiation was compared with no irradiation,[25] and in the NSABP B-24 trial breast irradiation plus tamoxifen was compared with breast irradiation plus placebo.[26] In both of these studies the presence of positive margins was associated with an approximate two-fold increase in the rates of local breast cancer recurrence. Thus, based on these considerations when involved margins are found, further revision or mastectomy is indicated. In the situation where a surgical margin remains positive, even after a revision, then mastectomy should be considered.

It has been reported that microscopic features such as a poor nuclear grade, large tumour size or extensive intraductal component (EIC) of the tumour are associated with a higher likelihood of local recurrence (see **guideline 6**).[27] However, their presence generally is not a contraindication to lumpectomy. Most of the evidence associating EIC with local recurrence comes from case series in which margins were not well controlled or evaluated.[28–32] In series in which margins were well controlled, EIC was consistently found not to be predictive of local recurrence.[11,33–37] The treatment of ductal carcinoma in situ is the subject of a separate guideline (**guideline 5**).

Contraindications to radiotherapy

In the absence of contraindications, radiotherapy should be a standard adjunct to BCS. In the NSABP trial of BCS versus mastectomy, at 12 years of follow-up the cumulative rates of recurrence following BCS were 10% among those who received radiotherapy and 35% among those who did not (level I evidence).[5] However, physical disabilities may prevent the use of radiotherapy; for example, if the patient cannot lie flat, abduct the arm to 90° or place the hand on the

forehead. Contraindications to radiotherapy include pregnancy or previous therapeutic irradiation of the breast or thorax. Women in the third trimester may undergo adjuvant radiotherapy after delivery. There may also be relative contraindications such as a history of systemic lupus erythematosus or scleroderma (see **guideline 6**). If any of the above situations is present, women should be made aware that the risk of local recurrence is increased without radiotherapy and that this can be avoided by mastectomy.

Large tumour mass

Cosmetic results of BCS depend on the proportion of breast removed, not on the absolute volume of excised tissue. Rarely, a tumour in a small breast may be so large as to preclude an acceptable cosmetic result with BCS. In this situation mastectomy should be recommended.

- **The following factors are not contraindications for BCS: the presence of a centrally located tumour mass, axillary lymph-node involvement or the presence of breast implants.**

Centrally located tumours

Central lesions carry the same overall prognosis as lateral lesions (level III evidence) and are not a contraindication to BCS.[38] These lesions should be removed in the same fashion as peripheral lesions. This may mean removal of part or all of the nipple or areola if necessary. The primary goal of BCS should be the achievement of clear margins. Even though extra tissue is removed, the shape, sensation and contour resulting from BCS are still generally superior to those of a reconstructed breast. The nipple may be reconstructed if desired (level IV evidence).

Lymph-node involvement

Studies have shown no difference in survival between mastectomy and BCS plus radiation therapy among women with either node-positive or node-negative breast cancer (level I evidence).[5]

Breast implants

The presence of a prosthesis is *not* a contraindication to BCS provided that the tumour can be removed with clear margins without damaging the prosthesis. Neither is a prosthesis a contraindication to radiotherapy;[39] however, radiotherapy probably does increase the risk of fibrotic reaction around a prosthesis (level IV evidence).[40]

Preoperative (neoadjuvant) chemotherapy for operable breast cancer

- **In some cases, preoperative chemotherapy can shrink a large primary tumour and allow for BCS.**

The concept of using preoperative chemotherapy in women with operable breast cancer is supported by several observations. First, in experimental animal studies, removal of the primary tumour resulted in an increased growth of metastases, and this alteration in growth kinetics of the secondary tumours could be prevented by the administration of chemotherapy before removal of the primary tumour.[41] Second, chemotherapy administered for locally advanced breast cancer could result in substantial shrinkage of tumours such that previously unresectable tumours could now be surgically resected.[42–44]

Two trials have evaluated preoperative chemotherapy compared with the same chemotherapy given postoperatively in women with early breast cancer.[45–48] In the NSABP B-18 trial, the primary objective was to determine whether preoperative chemotherapy (four cycles of adriamycin and cyclophosphamide) could improve disease-free survival and overall survival compared with the same chemotherapy administered following surgery.[45–47] Over 1500 women participated in this trial, and at 5 years of follow-up no difference was detected between treatment groups in both disease-free and overall survival.

Secondary aims of the trial were to determine whether preoperative chemotherapy resulted in more women undergoing BCS, and to examine the relation between response to chemotherapy and disease-free and overall survival. Sixty-seven percent of the women in the preoperative chemotherapy group underwent lumpectomy, compared with 60% in the postoperative chemotherapy group ($p = 0.002$). Among women with tumours > 5cm in diameter, the rates of lumpectomy were 22% versus 8%, respectively. The overall response rate to preoperative chemotherapy was 80% (36% of patients achieved a complete clinical response and 44% a partial response). Of the women with a complete clinical response, 26% had a complete pathologic response. Women with both complete pathologic and clinical responses had better disease-free and overall survival than women whose tumours did not shrink with preoperative chemotherapy.

The results of the NSABP B-18 trial were recently updated through 9 years of follow-up.[47] The 9-year disease-free survival was 55% in the preoperative group and 53% in the postoperative group. The corresponding rates for overall survival were 69% and 70%. There was a trend toward a higher rate of local breast cancer recurrence among the lumpectomy patients who received preoperative chemotherapy than among those who received postoperative chemotherapy (10.7% v. 7.6%) ($p = 0.12$). In the preoperative chemotherapy group, the rate of local breast cancer recurrence was 15.9% among the 69 patients who underwent lumpectomy instead of the originally planned mastectomy, compared with 9.9% among the 434 patients who underwent lumpectomy as originally planned ($p = 0.04$).

In a trial conducted by the EORTC, 698 women with breast cancer were randomly assigned to 4 cycles of fluorouracil, epirubicin and cyclophosphamide either preoperatively or postoperatively.[48] At a median follow-up of 56 months no difference was detected between the groups in disease-free or overall survival.

An overall objective response was observed in 49% of patients in the preoperative chemotherapy group; 23 patients (6.6%) experienced a complete clinical response. In the preoperative chemotherapy group, 189 patients were scheduled to have a modified radical mastectomy, and 57 (23%) underwent BCS. Of the 77 scheduled to undergo BCS, 14 (18%) underwent mastectomy. On subgroup analysis, patients who were scheduled to have mastectomy but whose disease was downstaged to breast conservation therapy had worse survival than patients who underwent lumpectomy as initially planned.

In conclusion, preoperative chemotherapy does not improve disease-free or overall survival compared with the more traditional approach of postoperative adjuvant chemotherapy. In some instances, preoperative chemotherapy can shrink a large primary tumour and allow for BCS. However, in such circumstances there may be an increased risk of local breast cancer recurrence following breast irradiation. If preoperative chemotherapy is being considered, there are certain surgical issues that must be addressed.[44] The first relates to the ability to identify the exact tumour location when a complete clinical response has occurred. The second relates to the amount of breast tissue that needs to be removed during lumpectomy in responding patients.

Informed choice

- **Before deciding between BCS and mastectomy, the physician must make a full and balanced presentation to the patient concerning the pros and cons of these procedures.**

The body shape is less disturbed after BCS than after mastectomy,[49–51] and fewer women experience disruption of their sexual relationships.[49,51] However, there is evidence that overall psychological morbidity and quality of life are similar whether women are treated with BCS or mastectomy.[49–53] The dominant concern is often fear of cancer recurrence rather than fear of losing the breast.[54] In a prospective study involving 269 patients, those whose surgeons offered them a choice between BCS and mastectomy were less likely to have depression than those whose surgeons did not offer them a choice, independent of the type of surgery performed.[54] This emphasizes the importance of involving patients in the decision-making process.[55,56]

Surgical technique

Nearly all mammographically detected cancers and at least 80% of clinically detected cancers are suitable for breast conservation.[57] Presented below are some of the key technical surgical points that have the endorsement of experienced surgeons in this specialized field (level IV evidence).[58]

- **Whenever an open biopsy is performed on the basis of even modest suspicion of carcinoma, the procedure should be, in effect, a lumpectomy, using wide local excision of the intact tumour surrounded by a cuff of tumour-free tissue (determined by palpation**

and visual inspection).

Many of these tumours can be adequately excised with clear margins at the first session, avoiding the need for a second operation. When this result is not achieved and a biopsy specimen is later reported as containing malignant cells, a second operation is required to excise the tumour or tumour-bearing area and reassess the margins. In this situation, blood and serum will be present in the cavity, discolouring the surrounding normal tissues and causing reactive induration, with the result that the subsequent excision is not as easy to accomplish and pathological evaluation is not as accurate. The best operation balances the primary need to remove the tumour completely against the secondary goal of achieving the best cosmetic result. Removal of an excessive amount of breast tissue, as in a quadrantectomy, is associated with reduced local recurrence but also with poorer cosmetic results. It has no advantages in terms of avoidance of metastases or death from cancer.[15]

A clear margin is one with no malignant cells at the cut surface on microscopic examination. In the NSABP clinical trial results described earlier, clear margins were obtained but no minimum width was required. At operation, the limits of the tumour can usually be identified on gross inspection. Although frozen section can be useful for the initial evaluation of 1 or 2 uncertain areas, the detailed analysis required for good margin evaluation cannot be accomplished by the frozen-section technique.

The specimen should be oriented for the pathologist, using marking sutures or radiolucent clips. Skin removal is not necessary unless the tumour is immediately subdermal. The pathologist should use the established techniques for painting and assessing the margins.

- **The following recommendations should be observed to provide optimum clinical and cosmetic results:**

    a. **tumour-involved margins should be revised;**
    b. **separate incisions should be used for removal of the primary tumour and for the axillary dissection except when these coincide anatomically;**
    c. **curvilinear incisions, concentric with the areolar margin, or transverse incisions are recommended over radial incisions;**
    d. **drains and approximation sutures should not be used in the breast parenchyma.**

If the final pathology report indicates the presence of unsuspected margin involvement, the margins should be revised by opening the original incision and removing several additional millimetres of tissue from the affected margins. Exceptions may be considered when such intervention would cause significantly poorer cosmesis. Of course, the patient must fully understand that local recurrence may be more likely. As noted above, persistent marginal involvement after revision should lead to consideration of mastectomy.

Separate incisions should be used for removal of the primary tumour and for the axillary dissection except where these happen to coincide anatomically: The lumpectomy incision should be placed directly over the lesion. Tunnelling from a circumareolar incision to a more peripheral lesion raises the danger of incomplete removal and should be avoided. Also, a single incision that is extended to reach the axilla will produce distorted and contracted scars. Generally, incisions should not extend outside the radiotherapy field (midsternum to midaxillary line).

Curvilinear incisions, concentric with the areolar margin, or transverse incisions are recommended over radial incisions: Subareolar tumours should be removed through circumareolar incisions. Tunnelling should be avoided. In the upper or lower part of the breast, radial incisions give poor cosmetic results; curvilinear or transverse incisions should be used. If an ellipse of skin must be removed from inferior to the areola, a radial incision may minimize inferior deflection of the nipple and areola.[58,59]

Drains should not be used in the breast and approximation sutures should not be used in the breast parenchyma. In the absence of drainage and approximation sutures the cavity fills with normal wound-healing elements, and the eventual consistency of the breast may be indistinguishable from normal tissue.

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Table 1: Summary of survival and recurrence in prospective randomized trials of mastectomy versus breast-conserving surgery

Study group	Intervention	No. of patients	Follow-up, yr	Overall survival, %	Disease-free survival, %	Local recurrence, %
Veronesi et al (Milan), 1990[8]	BCS + RT TM	352 349	15 15	68 66	— —	3.3 2.3
Fisher et al (NSABP), 1995[5]	BCS BCS + RT TM	634 628 589	12 12 12	58 62 60	47 49 50	35 10 8
Blichert-Toft et al (Denmark), 1992[3]	BCS + RT TM	430 429	6 6	79 82	70 66	— —
Van Dongen et al (EORTC), 2000[6]	BCS + RT TM	466 436	10 10	65 66	— —	20 12
Jacobson et al (NCI), 1995[9]	BCS + RT TM	121 116	10 10	77 75	72 69	5 10
Arriagada et al (Institut Gustave-Roussy), 1996[2]	BCS + RT TM	88 91	15 15	73 65	55 44	9 14

Note: NSABP = National Surgical Adjuvant Breast Project, NCI = National Cancer Institute, EORTC = European Organization for the Research and Treatment of Cancer, BCS = breast-conserving surgery, RT = radiotherapy, TM = total mastectomy.