Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update)

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This article provides a summary of the changes along with the updated recommendations (Table 1) made by Health Canada's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer to the article "Clinical Practice Guidelines for the Care and Treatment of Breast Cancer: 6. Breast radiotherapy after breast-conserving surgery," originally published in 1998[1] (the 2003 update can be found online at www.cmaj.ca/cgi/content/full/158/3/DC1).

In the 1998 guideline, irradiation to the whole breast following breast-conserving surgery (BCS) was recommended. This recommendation was based on the results of 5 randomized trials that demonstrated that postoperative breast irradiation substantially reduced the risk of recurrent cancer in the breast compared with no irradiation. In the 2003 update, results of longer follow-up from 2 of these trials are presented.[2,3] There continues to be a statistically significant reduction in breast cancer recurrence associated with irradiation. In a Scandinavian trial, at 10 years of follow-up, the rate of local recurrence was 8.5% in the irradiation group compared with 24% in the no treatment group.[2] In an Italian trial, at a median of 9 years of follow-up, the corresponding rates were 5.8% and 23.5%.[3] There was one new trial reported that compared breast irradiation following BCS with no irradiation. In this trial, from Finland, 152 women over 40 years of age with node-negative breast cancer whose tumours were smaller than 2 cm in diameter were randomly assigned to BCS followed by radiation therapy or BCS alone.[4] At 6.7 years of follow-up, the local recurrence rate was 7.5% in the irradiated group and 18.1% in the control group (p = 0.03). Hence, our 1998 recommendation concerning the administration of radiation after BCS has not changed.

A frequently asked question is whether any patients who undergo BCS are at such a low risk of local recurrence (e.g., those with small tumours and older women) that they do not require irradiation. Data recently reported from 3 randomized trials addressed this issue. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial, 1009 women with node-negative breast cancer and tu-

Table 1: Updated recommendations from the clinical practice guideline for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (BCS)

- Women who undergo BCS should be advised to have postoperative breast irradiation. Omission of radiation therapy after BCS increases the risk of local recurrence.
- Contraindications to breast irradiation include pregnancy, previous breast irradiation (including mantle irradiation for Hodgkin's disease) and inability to lie flat or to abduct the arm. Scleroderma and systemic lupus erythematosus are relative contraindications.
- A number of different fractionation schedules for breast irradiation have been used. Although the most common fractionation schedule in Canada to date has been 50 Gy in 25 fractions, recent data from a Canadian trial demonstrate that 42.5 Gy in 16 fractions is as good as this more traditional schedule.
- Irradiation to the whole breast rather than partial breast irradiation is recommended.
- There is insufficient evidence to recommend breast irradiation with brachytherapy implants or intraoperative radiation therapy. Further evaluation of these treatments in randomized trials is required.
- Additional irradiation to the lumpectomy site (boost irradiation) reduces local recurrence but can be associated with worse cosmesis compared with no boost. A boost following breast irradiation may be considered in women at high risk of local recurrence.
- Physicians should adhere to standard treatment regimens to minimize the adverse effects of breast irradiation.
- When choices are being made between different treatment options, patients must be made aware of the acute and late complications that can result from radiation therapy.
- Breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiation therapy is preceded by chemotherapy. However, the optimal interval between BCS and the start of irradiation has not been defined.
- The optimal sequencing of chemotherapy and breast irradiation is not clearly defined for patients who are also candidates for chemotherapy. Most centres favour the administration of chemotherapy before radiation therapy. Selected chemotherapy regimens are sometimes used concurrently with radiation therapy. There is no evidence that concurrent treatment results in a better outcome, and there is an increased chance of toxic effects, especially with anthracycline-containing regimens.
- Patients should be offered the opportunity to participate in clinical trials whenever possible.

mours 1 cm in diameter or smaller treated by BCS were randomly allocated to receive tamoxifen alone, breast irradiation alone or tamoxifen plus breast irradiation.[5] About 80% of the women were 50 years of age or older. The average follow-up was 7.2 years. The rate of local breast recurrence at 8 years was 16.5% with tamoxifen alone, 9.3% with irradiation alone and 2.8% with tamoxifen plus irradiation ($p < 0.01$ for all comparisons).

In a Canadian trial, 769 women over 50 years of age (median age 68 years) with tumours less than 5 cm in diameter and pathologically or clinically node-negative were randomly assigned after BCS to receive tamoxifen or tamoxifen plus breast irradiation.[6] The median follow-up was 3.4 years. The rate of local recurrence at 4 years was 6% in the tamoxifen group and 0.3% in the tamoxifen plus irradiation group ($p = 0.009$). In an Intergroup trial, 647 women 70 years of age or older with estrogen-receptor (ER) positive tumours less than 2 cm in diameter and pathologically or clinically node-negative were randomly assigned after BCS to tamoxifen or tamoxifen plus breast irradiation.[7] The median follow-up was 2.3 years. The annual rate of local recurrence was 0.9% with tamoxifen alone and 0% with tamoxifen plus breast irradiation ($p > 0.05$).

The steering committee feels that the results of the NSABP trial indicate that the risk of local breast cancer recurrence in patients who received tamoxifen without irradiation is high. Although the results of the Canadian and Intergroup trials suggest that older women with small ER-positive tumours who receive tamoxifen without breast irradiation may have a lower risk of recurrence, the follow-up is still too short. Thus, breast irradiation should not be omitted.

A commonly used radiation fractionation schedule in Canada has been 50 Gy in 25 fractions to the whole breast without a boost (i.e., without additional radiation to the lumpectomy cavity) when the margins of surgical excision are clear of disease.[8] The results of a Canadian trial have recently been reported in which women with node-negative breast cancer who underwent BCS were randomly assigned to either the more traditional, longer course of breast irradiation (50 Gy in 25 fractions administered over 35 days) or a shorter course (42.5 Gy in 16 fractions over 22 days).[9] The median follow-up was 5.8 years. No difference was detected in the rates of local recurrence or cosmetic outcome at 5 years between the treatment groups. The rates of local breast recurrence were 3.2% in the long treatment arm and 2.8% in the short treatment arm. The steering committee supports the use of the shorter irradiation schedule in most patients. A number of centres in Canada have already switched to this shorter fractionation course.

The steering committee also considered the issue of boost irradiation to the breast. In the 1998 guideline, the data considered were from case series. In the current update, the results of 3 randomized trials are reported. In a trial from France, 1024 patients with tumours 3 cm in diameter or smaller and clear margins following BCS were randomly allocated to receive breast irradiation plus a boost to the primary site or breast irradiation alone.[10] The median follow-up was 3.3 years. The rate of local recurrence at 5 years was 3.6% in the boost group compared with 4.5% in the control group ($p = 0.044$). More patients in the boost group than in the control group had telangiectasia of the skin of the breast. In another trial from France, 664 patients who underwent BCS were randomly assigned to receive breast irradiation plus a boost or breast irradiation alone.[11] At a median follow-up of 6.1 years, the rate of local recurrence was 4.3% among patients who received the boost and 6.8% among those who did not ($p = 0.13$). The European Organization for Research and Treatment of Cancer (EORTC) conducted a trial involving 5318 women with early breast cancer who underwent BCS.[12] The median follow-up was 5.1 years. The rate of local recurrence at 5 years was 4.3% in the boost group compared with 7.3% in the control group ($p < 0.001$). An excellent or good cosmetic outcome was observed in 71% of the patients treated with a boost, compared with 86% of those in the control group ($p < 0.001$). Patients less than 50 years of age were at higher risk of local recurrence than older women, and in this group of patients the absolute benefit of a boost appeared greater.

The steering committee feels that the results of these studies support the notion that boost irradiation to the primary site in patients with clear resection margins reduces the risk of local recurrence. However, the absolute benefit is small, and the use of boost irradiation is associated with a decrease in cosmetic outcome. In the recent Canadian trial that compared different radiation therapy regimens,[9] when a boost was not administered the rates of local recurrence were very low (3.2% in the long treatment arm and 2.8% in the short treatment arm). These rates were lower than those in the boost arm of the EORTC trial. Hence, the steering committee feels that a boost following breast irradiation is not required in all women who undergo BCS but might be considered in women at particularly high risk of local recurrence (e.g., those less than 40 years of age or those with positive or close resection margins).

The steering committee also considered the topic of brachytherapy implants (i.e., radioactive seeds placed into the tumour bed) or intraoperative radiation. Recently, a number of pilot studies have demonstrated that partial breast irradiation utilizing brachytherapy implants or local intraoperative radiation therapy may provide adequate local control with acceptable cosmetic outcome in selected patients.[13,14] However, none of these techniques has been evaluated in randomized trials. Thus, the steering committee feels that data from randomized trials are necessary before definitive recommendations about these treatments can be made.

Since the publication of the 1998 guideline, a number of studies have evaluated the acute and long-term morbidity of breast irradiation. In the Canadian randomized trial,[15] breast irradiation was associated with a modest negative impact on quality of life during treatment and 1 month following treatment. This association was attributed to the

side effects of fatigue, skin irritation and the inconvenience of daily treatments. In the original guideline, studies of breast irradiation after lumpectomy had not shown an increase in long-term cardiac mortality. A recent Canadian study using data from a cancer registry suggested that the rate of death from myocardial infarction was increased by 1% at 10 years with irradiation of left-sided breast cancer.[16] A systematic evaluation of cardiac morbidity in a large number of women in the same cohort showed no increase.[17]

In summary, trials of breast irradiation following lumpectomy continue to support the evidence that irradiation substantially reduces the risk of local recurrence and prevents the need for mastectomy. Negative effects on acute and long-term morbidity appear to be limited.

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