Clinical practice guidelines for the care and treatment of breast cancer: 6. Breast radiotherapy after breast-conserving surgery (2003 update)

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[Patient guidelines available here]

Abstract

Objective: To help physicians and their patients arrive at optimal strategies for breast radiation therapy after breast-conserving surgery (BCS) for early breast cancer.

Outcomes: Local control, survival, quality of life, adverse effects of irradiation and cosmetic results.

Evidence: A literature search using MEDLINE from 1966 to October 2001 and CANCERLIT from 1983 to September 2001. A nonsystematic review of the literature was continued through April 2002.

Benefits: A decrease in local recurrence of breast cancer.

Harms: Adverse effects of breast irradiation.

Recommendations:

- 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.

Validation: The original guideline was updated by a writing committee, which then submitted it for review, revision and approval by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The current update did not undergo an external review.

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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Approximately 80% of women who present with breast cancer have lesions that are amenable to breast-conserving surgery (BCS). Randomized trials have shown that BCS is equivalent, in terms of survival, to mastectomy (see guideline 3), and the use of BCS is increasing.

A number of well-executed clinical trials evaluating the role of breast irradiation after BCS have been completed. These guidelines, which incorporate this information, are intended to assist the patient and her physician(s) in making the most clinically effective and personally acceptable choices concerning the use of breast irradiation after BCS for invasive breast cancer. The management of ductal carcinoma in situ (DCIS) is addressed in a separate guideline (guideline 5). The question of axillary node irradiation is not addressed in this document.

Methods

The evidence reviewed for this document was retrieved through a systematic review of the English-language literature using MEDLINE from 1966 to October 2001 and CANCERLIT from 1983 to September 2001. Search terms included the following: "breast neoplasms," "segmental mastectomy," "lumpectomy," "breast conservation," "radiotherapy," "irradiation," "clinical trials," "practice guidelines" and "meta-analysis." Bibliographies from recently published reviews were scanned and relevant articles retrieved. A nonsystematic review of the literature and monitoring of major conferences on breast cancer were continued through April 2002.

The quality of the evidence on which conclusions are based is categorized into 5 levels.[1] The initial draft of the original guideline was based on the report "Evidence based recommendation report for breast irradiation following breast conserving surgery," prepared for the Cancer Care Ontario Breast Disease Site Group. The iterative process used to develop the original guideline has been described previously.[2] A writing committee updated the original guideline and then 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)

The role of radiation therapy after 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.**

There is substantial level I evidence that breast irradiation after BCS reduces the incidence of local recurrence, providing a survival rate equivalent to that of mastectomy[3–14] (Table 1).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, 2105 women with node-negative or node-positive breast cancer and tumours 4 cm or less in diameter were randomly assigned to 1 of 3 treatment arms: (a) modified radical mastectomy, (b) lumpectomy plus axillary dissection followed by local breast irradiation or (c)

lumpectomy and axillary dissection alone.[3–5] There was no difference in survival between the 3 treatment groups at an average follow-up of 12 years.[5] However, the rate of local recurrence was substantially lower among all patients who received a lumpectomy plus local breast irradiation of 50 Gy over 5 weeks to the whole breast than among patients who were treated with lumpectomy alone (10% v. 35%, $p < 0.001$).[5] For patients with node-negative disease treated by lumpectomy, the rate of local recurrence among those who received adjuvant radiation therapy was 12% compared with 32% among those who received no adjuvant radiation therapy. For patients with node-positive disease (all of whom also received chemotherapy), the rates of local recurrence with and without adjuvant radiation therapy were 5% and 41% respectively (level I evidence).

In another study, carried out in Sweden, 381 women with node-negative breast cancer and primary tumours 2 cm or less in diameter were randomly assigned after sector resection to receive either breast irradiation (54 Gy in 27 fractions to the whole breast) or no breast irradiation.[6–8] At 10 years' follow-up, the local recurrence rate was lower among those who received irradiation than among those who did not (8.5% v. 24%, $p = 0.0001$) (level I evidence).[8] There was no difference in survival between the 2 treatment groups.

In a Canadian study, 837 patients with node-negative disease who underwent lumpectomy were randomly assigned to receive either no breast irradiation or breast irradiation (40 Gy in 16 fractions over 3 weeks to the whole breast, plus a local boost of 12.5 Gy in 5 fractions over 1 week to the primary site).[9,10] The rate of local recurrence at a median of 7.6 years of follow-up was 35% in the non-irradiated group compared with 11% in the irradiated group ($p < 0.001$) (level I evidence).[10] No difference in survival was detected between the 2 groups.

In an Italian trial, 567 women with either node-negative or node-positive tumours less than 2.5 cm in diameter were randomly assigned to undergo either quadrantectomy followed by breast irradiation (50 Gy in 5 weeks to the whole breast, plus a boost to the tumour bed of 10 Gy in 5 fractions) or quadrantectomy without radiation therapy.[11] At a median follow-up of 9 years the rates of local recurrence were 5.8% in the irradiated group and 23.5% in the non-irradiated group ($p < 0.001$) (level I evidence). There was no difference in overall survival between the 2 groups.[12]

In another trial, in Scotland, 585 women with primary breast cancers 4 cm or less in diameter were randomly assigned after BCS and systemic therapy to receive either 50 Gy in 20 to 25 fractions to the breast with a boost to the tumour bed, or no radiation therapy.[13] At 6 years, local breast recurrence rates were much lower in the irradiated group than in the non-irradiated group (5.8% v. 24.5%) (level I evidence). No difference was detected in survival between the groups.

In a study conducted in Finland, 152 women over 40 years of age who had node-negative breast tumours smaller than 2 cm in diameter were randomly assigned to lumpectomy alone or to lumpectomy followed by radiation therapy (50 Gy in 5 weeks) to the ipsilateral breast.[14] 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 ($p = 0.03$) (level I evidence). There was no difference in overall 5-year cancer-specific survival between the groups.

The 1995 update of the meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) included 4 of the published trials and 2 unpublished trials involving over 4000 patients. The results are consistent with the findings of the 6 studies reported above. There was a 68% reduction in risk of local recurrence after radiation therapy but no significant impact on overall survival (level I evidence).[15] The EBCTCG met in the fall of 2000, and their updated analysis should be available in the future.

In most of these trials, local relapse was treated by mastectomy despite a policy of re-excision followed by breast irradiation for local relapse in patients treated by lumpectomy alone.[6,9,11] The Swedish study[6] reported an overall mastectomy rate for local recurrence of 70%, the Canadian trial[9] reported a mastectomy rate of approximately 50%, and the Italian study[11] reported a mastectomy rate of 40%.

Are there any situations that confer so low a risk of recurrence that irradiation can safely be omitted? The probability of local recurrence without radiation therapy is less when tumours are small (< 2 cm in diameter) and when women are older than 50 years of age. However, omission of irradiation after BCS increases the risk of local recurrence, even in these cases. The Canadian study that evaluated the role of breast irradiation after lumpectomy in patients with node-negative breast cancer found that women aged 50 years and older who had tumours 2 cm or less in diameter were possibly a low-risk group.[9] However, the rate of local relapse among such women treated by lumpectomy alone was 22%.[10] Similarly, in the NSABP B-06 study, although tumour size predicted local recurrence in the breast, the risk of recurrence after BCS among patients with node-negative disease with tumours 1 cm or less in diameter who did not receive radiation therapy was still 25% (level III evidence).[16] It has been postulated that patients who undergo more extensive resection of the tumour my be at somewhat lower risk of recurrence. However, the results of the Milan and Uppsala-Örebro trials do not support this hypothesis. In the former trial, women who underwent quadrantectomy without radiation therapy had a local recurrence rate of 23.5%.[12] In the Swedish trial, patients who underwent sector resection without radiation therapy had a rate of 24%.[8]

Investigators have evaluated the role of chemotherapy without irradiation in preventing local recurrence after BCS. An Ontario study involving patients with node-positive disease identified a subset of 121 premenopausal patients who had undergone BCS and for whom no breast irradiation was given but who had received a 12- or 36-week course of systemic adjuvant chemotherapy. The rate of local recurrence was lower after the longer, 36-week systemic treatment with the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) plus vincristine and prednisone (CMFVP) than after 12 weeks of treatment (23% v. 39%, $p = 0.02$). However, these recurrence rates were not sufficiently reduced to justify replacement of breast irradiation with chemotherapy alone.[17] In the trial from the Scottish Cancer Trials Breast Group, 585 women who underwent BCS were randomly assigned to receive or not receive radiation therapy. All received systemic therapy, with either tamoxifen or intravenously administered CMF according to the estrogen receptor status of the tumour. The local relapse rate among those receiving radiation therapy was 5.8% compared with 24.5% among those who did not receive radiation therapy (level I evidence).[13]

Recently, several trials have investigated the role of tamoxifen alone after lumpectomy in women considered to be at lower risk of local recurrence. In the NSABP B-21 trial, 1009 women with node-negative breast cancer and tumours 1 cm in diameter or smaller treated by lumpectomy were randomly assigned to receive tamoxifen alone, breast irradiation alone or tamoxifen plus breast irradiation. 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 radiation alone and 2.8% with tamoxifen plus irradiation ($p < 0.01$ for all comparisons) (level I evidence).[18] Overall survival was not significantly different between the treatment arms.

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 lumpectomy to receive tamoxifen (20 mg/d for 5 years) or tamoxifen plus breast irradiation.[19] 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 over with estrogen-receptor (ER) positive tumours less than 2 cm in diameter and pathologically or clinically node-negative were randomly assigned after lumpectomy to receive tamoxifen or tamoxifen plus breast irradiation. The median follow-up was 2.3 years. The annual rate of locoregional recurrence was 0.9% with tamoxifen alone and 0% with tamoxifen plus irradiation ($p > 0.05$).[20]

In summary, the results of the NSABP trial indicate that the risk of local breast cancer recurrence in patients who receive tamoxifen without irradiation is high. 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, but follow-up is still too early to recommend that radiation therapy not be given.

Contraindications to breast irradiation

- **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.**

For some patients, physical disabilities, such as inability to lie flat or adequately abduct the arm, can make irradiation difficult or impossible. Also, previous high-dose irradiation to the thorax precludes further radiation therapy. Increased rates of acute and late radiation effects have been reported among patients with pre-existing collagen vascular disease, including scleroderma and systemic lupus erythematosus.[21,22] Although a study involving 122 patients using a matched cohort design suggested no statistical difference in acute or late complications between patients with collagen vascular disease and normal controls, the power to detect a difference was low and a proportion of the cases in the collagen vascular disease group in fact had rheumatoid arthritis, which is not considered a contraindication to irradiation.[23] Thus, based on present evidence, scleroderma and systemic lupus erythematosus should be considered relative contraindications to radiation therapy. When these conditions are present, women should be made aware that the risk of local recurrence is increased without radiation therapy and that this outcome can be avoided by mastectomy.

Radiation techniques

- **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.**

In planning therapy, the 2 main considerations are controlling local recurrence and obtaining a satisfactory cosmetic outcome. In the 6 randomized trials of breast irradiation versus no irradiation after lumpectomy already discussed, [3–14] only 2 used the same radiation fractionation schedule[5,14] (Table 1). Fractionation schedules used in these trials ranged from 40 Gy in 16 fractions to 54 Gy in 27 fractions administered to the whole breast with or without boost irradiation to the primary site. Each fraction of radiation was delivered daily Monday to Friday. In patients with comparable stages of breast cancer and similar lengths of follow-up, the rates of local recurrence were similar (level III evidence). Prospective and retrospective cohort studies have also reported acceptable rates of local control and cosmesis with similar fractionation schedules.[24–28]

A commonly used fractionation schedule in Canada has been 50 Gy in 25 fractions to the whole breast without boost irradiation when the margins of surgical excision are clear of disease (the same schedule used in the NSABP studies). [29] The Ontario Clinical Oncology Group (OCOG) recently reported the results of a Canadian randomized trial in which the more traditional, longer course (50 Gy in 25 fractions administered over 35 days) was compared with a shorter course (42.5 Gy in 16 fractions over 22 days) in women with node-negative breast cancer following lumpectomy.[30] Ten cancer centres in Ontario and Quebec and 1234 women participated in the trial. The median follow-up was 5.8 years. No difference was detected in the rates of local recurrence or cosmetic outcome at 5 years (level I evidence). The rates of local breast recurrence were 3.2% in the long treatment arm and 2.8% in the short treatment arm (absolute difference 0.4%, 95% confidence interval –1.5% to 2.4%). The trial was limited to patients whose breast was less than 25 cm in width at the midpoint of the radiation field. It is unclear whether the results of this study apply to women with larger breasts, who may be more prone to poor cosmetic outcome when radiation techniques are not optimized. Although the trial was restricted to patients with node-negative disease, the observed results are likely generalizable to patients with node-positive disease.

- **Irradiation to the whole breast rather than partial breast irradiation is recommended.**

In a trial comparing irradiation to the whole breast and partial breast irradiation, 708 patients were randomly assigned after BCS to receive either whole or partial breast irradiation.[24,31] At a median follow-up of 8 years, local relapse rates were 13% in the whole breast irradiation group and 25% in the partial breast irradiation group ($p = 0.00008$) (level I evidence).

- **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.**

Recently there have been a number of phase I and II studies demonstrating that partial breast irradiation with brachytherapy implants may provide adequate local control with acceptable cosmetic outcome in selected patients.[32,33] Local intraoperative radiation therapy is also being evaluated.[34] Further data from randomized trials are necessary before making definitive recommendations about the role of brachytherapy alone or intraoperative radiation therapy following lumpectomy.

- **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.**

The role of additional irradiation to the lumpectomy cavity, called boost irradiation, has been evaluated in 3 randomized trials (Table 2). In the Lyon trial, 1024 patients with tumours 3 cm in diameter or smaller and clear margins following lumpectomy were randomly assigned to receive radiation therapy with 50 Gy in 20 fractions over 5 weeks to the whole breast plus a boost to the primary site of 10 Gy in 4 fractions over 1 week or radiation therapy with 50 Gy in 20 fractions over 5 weeks to the whole breast with no boost.[35] The boost was delivered by a direct field using 9 or 12 MeV electrons. Approximately 50% of the patients received adjuvant chemotherapy or tamoxifen. The median follow-up was 3.3 years. The rate of local recurrence at 5 years was 3.6% among patients who received the boost and 4.5% among those who did not ($p = 0.044$) (level I evidence). More patients in the boost group than in the control group had telangiectasia (12.4% v. 5.9%, $p = 0.003$). No difference in survival was detected between the groups.

In the Nice trial, 664 patients with invasive breast cancer treated by lumpectomy were randomly assigned to receive radiation therapy with 50 Gy in 5 weeks plus a boost of 10 Gy in 1 week or radiation therapy with 50 Gy in 5 weeks alone.[36] The boost was delivered by electron beam or reduced cobalt tangents. 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 ($p = 0.13$) (level II evidence).

The European Organization for Research and Treatment of Cancer (EORTC) conducted a trial involving 5318 patients with early breast cancer who had clear resection margins following lumpectomy.[37,38] Patients were randomly assigned to receive radiation therapy with 50 Gy in 25 fractions to the whole breast plus a boost to the primary site of 16 Gy in 8 fractions, using an external beam (direct electrons, tangent photons) or brachytherapy, or radiation therapy with 50 Gy in 25 fractions to the whole breast alone. Approximately 80% of the patients had node-negative disease and 28% received adjuvant systemic therapy. The median follow-up was 5.1 years. The rate of local recurrence at 5 years was 4.3% among patients who received the boost and 7.3% among those who did not ($p < 0.001$) (level I evidence). No difference was detected in survival between the 2 groups. A good or excellent cosmetic outcome was produced in 71% of the patients who received the boost, compared with 86% of those who did not ($p < 0.001$).

Patients less than 50 years old were at higher risk of local recurrence than were older women, and in this group of patients the absolute benefit of a boost appeared greater.

The results of these studies indicate 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 a boost is associated with a poorer cosmetic outcome. Results of the EORTC study suggest that the absolute benefit may be in the order of 4%–10% for women less than 50 years of age. In the Canadian trial the rates of local breast recurrence were very low (3.2% in the long treatment arm and 2.8% in the short treatment arm).[30] These rates are lower than the rate in the boost arm of the EORTC trial. Among women less than 50 years of age in the Canadian trial, the rates of local breast recurrence were 3.6% in the short treatment arm and 7.2% in the long treatment arm. For such women the potential benefit with boost irradiation would be of a relatively small magnitude.

Controversy also exists regarding further management when the pathologist reports microscopic involvement or close resection margins with invasive cancer or DCIS.[39–42] Patients with positive margins following lumpectomy are at increased risk of local recurrence, and re-excision or mastectomy should be considered, especially if there is more than focal involvement (see guideline 3). Patients should be informed when margins are involved, and if surgery is declined it is normal practice to recommend boost irradiation. Similarly, patients with close resection margins (i.e., tumour approaches this margin by 1–2 mm) may be at increased risk of local recurrence, but data are conflicting. The effectiveness of boost irradiation for positive or close resection margins remains unclear.

Oncologists may wish to consider the use of a boost (10–16 Gy in 4–8 fractions) in women at increased risk of local recurrence following breast irradiation alone (e.g., those < 40 years of age, or those with positive or close resection margins). Patients should be informed about the absolute benefits and risks.

- **Physicians should adhere to standard treatment regimens to minimize the adverse effects of breast irradiation.**

BCS followed by breast irradiation is associated with very few significant complications.[30] The frequency and severity of complications and poor cosmetic results increase with the use of unusual dosages or dosage schedules, or when regional node irradiation is used as well.[43]

Negative health effects of 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.**

Skin erythema and fatigue are common short-term side effects of radiation therapy.

The cause of fatigue is not known; it is maximal in the first few weeks to months after radiation therapy. Skin erythema and fatigue usually resolve completely within 3 to 6 months. Such symptoms and the inconvenience of radiation therapy can affect a patient's quality of life.[44] In the Canadian randomized trial that evaluated the role of breast irradiation after

lumpectomy,[44] patients' quality of life was assessed at baseline and at 1 and 2 months following randomization. Patients treated with radiation therapy had little change in quality of life over the 2-month period, whereas those who did not receive radiation therapy had steady improvement in quality of life. The difference between groups was statistically significant ($p = 0.0001$).

Mild and moderate long-term effects of irradiation are relatively rare.

During the first 2 years after surgery and radiation therapy, patients may experience skin irritation and intermittent pain in the breast.[27,45–47] These symptoms are usually self-limiting and seldom severe.[44] In the Canadian trial that compared radiation therapy and no radiation therapy after lumpectomy,[10,44] both skin irritation and breast pain were more frequent at 3 and 6 months after treatment in the patients who received radiation therapy than in the control patients. The proportion of patients with symptoms steadily decreased over time, so that at 2 years skin irritation was reported by only 7% of the patients and breast pain by 15% regardless of whether the patients received radiation therapy.[44]

Other effects that may be experienced up to 5 years after BCS followed by breast irradiation include mild breast erythema (6%), mild breast edema (3%), moderate or severe breast induration (2%), and mild (13%) or moderate to severe (1%) telangiectasia over the breast area.[27]

Lasting cosmetic sequelae of irradiation may become visible after the first year and progress for several years.

These sequelae do not appear to worsen significantly after approximately 3 years.[27,47,48] Evaluation of cosmetic outcome has primarily been based on physician evaluation in case series.[47–51] A satisfactory result is reported in 80%–95% of cases.[27,45,50,52,53] In the Canadian trial, patients were asked to report any trouble or upset regarding the appearance of the breast on a regular basis.[44] Breast irradiation did not increase the proportion of patients at 2 years who were troubled by the appearance of the treated breast (4.8% of patients in the irradiated and non-irradiated groups, $p = 0.62$).

In a study from British Columbia, cosmetic results were reported to be satisfactory by 89% of physicians and 96% of patients.[27] Localized fat necrosis was reported in 1%–8% of patients, particularly in high-boost areas. This side effect is self-limiting and harmless but may be confused with local recurrence.[27,53]

Severe long-term adverse effects of irradiation are rare.

Older case series in which women received breast and nodal irradiation reported the following rare complications (< 1%): pneumonitis, pericarditis, rib fracture, brachial plexopathy and arm edema.[51,52,54] However, many of these complications were associated with techniques involving regional nodal irradiation and large total doses and fraction sizes that are no longer in use. With current irradiation techniques following lumpectomy, such complications will probably occur extremely rarely, if at all.

Investigators have evaluated the risk of death from myocardial infarction following breast

irradiation after lumpectomy. Rutqvist and associates reported no increase in the risk of myocardial infarction related to left-sided versus right-sided cancers in a population-based cohort of 684 Swedish women who were treated with breast irradiation.[55] The median follow-up was 9 years. Similarly, in an institutional-based study, Nixon and associates reported no increase in cardiac deaths related to laterality among 745 patients followed for a minimum of 12 years following breast irradiation.[56] Paszat and colleagues reported the results of a population-based study involving 3006 patients treated in Ontario between 1982 and 1987.[57] They found that at 10 years' follow-up, 2% of the women who had received radiation therapy for left-sided cancer had a fatal myocardial infarction, compared with 1% of those who had been treated for right-sided cancer ($p = 0.02$). Recently, Vallis and colleagues reported on the risk of fatal and nonfatal myocardial infarction in a similar cohort of patients treated at the Princess Margaret Hospital between 1982 and 1989.[58] A total of 2128 patients were evaluated. Care was taken to review the diagnosis of myocardial infarction according to prespecified diagnostic criteria. At a median follow-up of 10.2 years, no excess in cardiac disease was identified among patients who had received radiation therapy for left-sided cancer compared with those who had been treated for right-sided cancer. Despite the overlap in the populations, the difference in the results of the 2 latter studies may reflect a different methodology used to identify myocardial events and potentially different radiation therapy practices at different centres; for example, regional radiation therapy was used in only about 8.5% of cases at the Princess Margaret Hospital during the study period.

In the recent meta-analysis by the EBCTCG, 20-year results from 40 randomized trials were evaluated (level I evidence).[15] Although a reduction in the rate of death from breast cancer was observed, an increase in cardiovascular deaths was demonstrated. The majority of trials contained in the analysis were trials of locoregional radiation therapy after mastectomy. In the trials of breast irradiation, a significant increase in cardiovascular deaths was not observed.

In a retrospective analysis involving 825 women taking part in randomized trials in Milan, Valagussa and associates reported a modest increase in the occurrence of cardiac failure among patients who received anthracycline-containing regimens and breast irradiation (4/501 patients receiving adriamycin v. 3/114 receiving adriamycin plus irradiation of the left breast).[59] In a study by Shapiro and colleagues, an increased risk of cardiac disease was demonstrated only among patients who received a moderate to large portion of irradiation to the heart and 450 mg/m^2 of doxorubicin.[60]

In summary, it is unlikely that irradiation to the left breast is associated with an increased risk of death from cardiac causes. Nonetheless, it would be prudent to exercise caution in treating women with left-sided breast cancers when radiation therapy may involve the anterior aspect of the heart.

The risk of malignant disease resulting from breast irradiation after BCS is very low.

It has been suggested that breast irradiation may cause an increase in 3 types of malignant disease: breast cancer, sarcoma and leukemia.

Breast cancer: In a case–control study involving women under 45 years of age, a marginally significant elevation in risk of contralateral breast cancer was found following breast

irradiation after mastectomy.[61] However, for most patients, other relevant risk factors such as family history and histologic subtype were not reported. Other studies have failed to show a connection between irradiation and contralateral breast cancer (level III evidence).[62–64] Thus, at present there is no convincing evidence to support any such association. Nevertheless, techniques should be used that minimize exposure of the opposite breast, especially in younger women (level IV evidence).

Sarcoma: Most reports regarding the association of sarcoma with radiation therapy have involved orthovoltage therapy and regional as well as local breast irradiation.[51] Current evidence suggests that the risk of radiation-associated soft-tissue sarcomas is approximately 1 in 1000 patients per decade of follow-up.[53,65]

Leukemia: In a case–control study involving 82 700 women with breast cancer diagnosed between 1973 and 1985, there appeared to be a significant increase in risk of acute nonlymphocytic leukemia after regional radiation therapy, which increased with increasing dosage. However, after the exclusion of patients treated with alkylating agents, the relative risk of leukemia attributable to radiation therapy alone was not statistically significant.[66]

Recently, the NASBP reported results from trials in which patients received adjuvant chemotherapy with doxorubicin and cyclophosphamide. Six trials involving 8533 patients contributed over 50 000 patient-years of follow-up. Thirty-nine cases of acute myeloid leukemia or myelodysplastic syndrome were observed. The incidence of leukemia or myelodysplastic syndrome was increased among patients who received more intensive chemotherapy (relative risk 6.72, $p = 0.0001$) or breast irradiation (relative risk 2.45, $p = 0.007$).[67] This is the first report of an increased risk of leukemia with breast irradiation among women who received chemotherapy.

If the risk of leukemia is increased because of breast irradiation, the magnitude of the increase in absolute terms is very small. Clearly, this cannot be considered a contraindication to postoperative radiation therapy.

Time interval between surgery and 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 timing of radiation therapy has been studied in a cohort study involving 436 patients. Patients who began radiation therapy more than 7 weeks after BCS appeared to be at greater risk of recurrence than patients receiving treatment earlier (14% v. 5%).[68] However, the interval between radiation therapy and surgery was not significant when other relevant factors were considered in a multivariate analysis (level V evidence). Likewise, in a study involving 653 patients with node-negative breast cancer who received a dose of 60 Gy or greater to the primary tumour site, when risk factors were controlled, there was no difference in the recurrence rates associated with intervals ranging from 4 to 8 weeks between surgery and radiation therapy (level V evidence).[69]

There remain a number of conflicting reports regarding the risk of recurrence following delay in radiation therapy after lumpectomy. Slotman and associates reviewed 508 cases of patients with stage I or II breast cancer treated with breast irradiation after lumpectomy (level V evidence).[70] At a median follow-up of 5.7 years, the rate of local recurrence was 1.7% among patients who started radiation within 7 weeks after surgery and 5.6% among those with a longer interval ($p < 0.05$). In a Cox proportional-hazard analysis, the interval between surgery and radiation remained predictive of local recurrence ($p = 0.003$). Froud and associates reviewed 1962 cases of women in British Columbia at low risk for recurrence who did not receive chemotherapy (level V evidence).[71] At a median follow-up of 5.9 years, they found no difference in ipsilateral breast recurrence for intervals between surgery and radiation therapy of 0–20 weeks. However, the risk of distant recurrence was significantly higher with intervals of more than 12 weeks between surgery and the start of radiation therapy.

In the absence of better evidence, any recommendation must rest on general principles. Thus, undue delay should be avoided. The Royal College of Radiologists of the United Kingdom set a maximum of 4 weeks as a target, but in a survey reported in 1995, only 55% of patients in the UK received radiation therapy within this interval.[72] However, the consensus of the contributors to this guideline is that 4 to 8 weeks may be a reasonable delay, but a delay of more than 12 weeks should be avoided except when chemotherapy is administered first.

Sequencing of chemotherapy and radiation therapy

- **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 better outcome, and there is an increased chance of toxic effects, especially with anthracycline-containing regimens.**

The issue of sequencing arises when breast irradiation and adjuvant chemotherapy are being planned. There are several options, including the delivery of all chemotherapy before radiation therapy; the delivery of radiation therapy before chemotherapy (both of these options are termed “sequential regimens”); the simultaneous institution of chemotherapy and radiation therapy (concurrent regimens); and the initiation of radiation therapy in the midst of a chemotherapy program (sandwich regimens). The choice may influence survival, disease-free survival and cosmetic outcome.

The 2001 update of a study by Recht and associates[73] reported the results for 244 patients treated with lumpectomy who were randomly assigned to receive radiation therapy before or after chemotherapy.[74] The median follow-up was 11.3 years. There was no significant difference in time to any failure, time to distant metastases or time to death between the 2 groups. The recurrence rates by site of first failure were also similar between the 2 groups (local recurrence 15% v. 13%, respectively; distant recurrence 26% v. 32%, respectively) (level II evidence). This study was relatively underpowered to detect differences in failure patterns. The timing of radiation therapy has been considered in other studies, with inconsistent results (level V evidence).[75–79]

In several trials designed to evaluate adjuvant chemotherapy regimens after BCS, radiation therapy was delayed until chemotherapy was completed, without any apparent increase in local recurrence (level I evidence).[80–83]

Apart from questions of survival and local recurrence, several case series have shown that when chemotherapy and radiation therapy are given concurrently, the potential for increased acute and late adverse effects of radiation therapy, including a worse cosmetic outcome, is increased.[83–85] This is especially so when anthracycline-based regimens are used (level III evidence).[84]

Clinical trials

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

As frequently noted above, the knowledge base for many of the interventions involved in the treatment of breast cancer is often extremely weak or does not exist. These particular areas of uncertainty, where recommendations must, at present, be based on level III, IV or V evidence, can be eliminated only by well-designed, randomized, controlled trials. Improvement in the care of future patients with breast cancer thus depends 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 patients should be given the chance to participate.

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Table 1: Summary of local recurrence and overall survival in randomized trials of breast irradiation after breast-conserving surgery

Study	Surgery	Length of follow-up, yr	Radiation treatment	No. of patients	Local recurrence, %	Overall survival, %
Fisher et al (NSABP B-06), 1995[5]	Lumpectomy	Mean 12	• 50 Gy over 5 wk	567	10	64
			• None	570	35	61
Liljegren et al (Uppsala-Örebro), 1999[8]	Sector resection	Median 9	• 54 Gy in 27 fractions	184	8.5	77.5
			• None	197	24	78
Clark et al (OCOG), 1996[10]	Lumpectomy	Median 7.6	• 40 Gy in 16 fractions over 3 wk plus boost of 12.5 Gy over 1 wk	416	11	79
			• None	421	35	76
Veronesi et al (Milan), 2001[12]	Quadrantectomy	Median 9	• 50 Gy over 5 wk plus boost of 10 Gy in 5 fractions	294	5.8	82.4
			• None	273	23.5	76.9
Forrest et al (Scotland), 1996[13]	Lumpectomy	Median 5.7	• 50 Gy in 20–25 fractions plus boost	291	5.8	83*
			• None	294	24.5	83*
Holli et al (Finland), 2001[14]	Lumpectomy	Mean 6.7	• 50 Gy over 5 wk	80	7.5	97.1†
			• None	72	18.1	98.6†

Note: NSABP = National Surgical Adjuvant Breast and Bowel Project, OCOG = Ontario Clinical Oncology Group.
*Estimated from published actuarial curve, hazard ratio 0.98, 95% confidence interval 0.67–1.44.
†Five-year cancer-specific survival rate.

Table 2: Summary of local recurrence and overall survival in randomized trials of boost irradiation following breast irradiation after breast-conserving surgery

Study	Median follow-up, yr	Radiation treatment	No. of patients	Local recurrence, %	Overall survival, %
Romestaing et al (Lyon), 1997[35]	3.3	• 50 Gy in 20 fractions over 5 wk • 50 Gy in 20 fractions over 5 wk + boost of 10 Gy in 4 fractions over 1 wk	503 521	4.5 3.6	90.4 92.9
Teissier et al (Nice), 1998[36]	6.1	• 50 Gy over 5 wk • 50 Gy over 5 wk + boost of 10 Gy over 1 wk	337 327	6.8 4.3	NA NA
EORTC[38]	5.1	• 50 Gy over 5 wk • 50 Gy over 5 wk + boost of 16 Gy in 8 fractions	2657 2661	7.3 4.3	91 91

Note: EORTC = European Organization for Research and Treatment of Cancer, NA = not available.