6. Breast radiotherapy after breast-conserving surgery

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

Abstract

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

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


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 radiotherapy after BCS almost always increases the risk of local recurrence.
- Contraindications to breast irradiation include pregnancy, previous breast irradiation (including mantle radiation for Hodgkin’s disease) and inability to lie flat or to abduct the arm. Scleroderma and systemic lupus erythematosus constitute relative contraindications.
- The commonest fractionation schedule used in Canada is 50 Gy in 25 fractions to the whole breast without a boost when excision margins are clear of disease. Alternative schedules that may be used range from 40 Gy in 16 fractions to the whole breast, with or without a boost, to 45 Gy in 25 fractions with a boost of 16 Gy in 8 fractions to the primary site. The role of boost irradiation to the primary site is unclear. Irradiation of the whole breast rather than partial irradiation is recommended.
- When choices are being made between different treatment options, patients must be made aware of the acute and late complications that can result from radiotherapy.
- Physicians should adhere to standard treatment regimens to minimize the adverse effects of irradiation.
- It is recommended that local breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiotherapy 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 irradiation is not clearly defined for patients who are also candidates for chemotherapy. Most centres favour the administration of chemotherapy before radiotherapy. Selected chemotherapy regimens are sometimes used concurrently with radiotherapy. There is no evidence that this results in better outcome, and there is an increased chance of toxic effects, especially for anthracycline-containing regimens.
- Patients should be offered the opportunity to participate in clinical trials whenever possible.

Validation: Earlier drafts of these guidelines were reviewed, discussed and approved by the Breast Disease Site Group of the Ontario Cancer Treatment and Research Foundation. They were next revised by a writing committee and by expert primary reviewers and secondary reviewers selected from all regions of Canada. The final version was approved by the Steering Committee and reflects a consensus of all these contributors. It has been endorsed by the Canadian Association of Radiologists.

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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 now been completed. These guidelines, which incorporate this information, are intended to assist the patient and her physicians 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 irradiation is not addressed in this document.

The principal objective of these guidelines is to facilitate informed decision-making. The importance of a sympathetic, clear and unhurried presentation of the issues has been stressed elsewhere (see guidelines 1, 2, 3, 5 and 9), as has the importance of good psychosocial support throughout the process of diagnosis and treatment (see guidelines 2 and 9).

**Method**

This guideline is the product of a process of iterative review and revision as described in the introduction. The initial draft was based on the report entitled Evidence based recommendation report for breast irradiation following breast conserving surgery prepared for the Ontario Provincial Disease Site Group by the same authors as listed on this guideline. The report was subsequently updated and published.1

This document was then reviewed by a writing committee consisting of 6 members of The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer and, after revision, submitted to 2 expert primary reviewers. It was again revised, reviewed by the Steering Committee and circulated to 15 secondary reviewers, consisting of family physicians, nurses, breast cancer patients, and surgical, medical and radiation oncologists from across Canada. Throughout, all changes were reviewed by Dr. Whelan. The revised document underwent final review and approval by the Steering Committee and thus represents a substantial consensus of all these contributors.

The evidence used is based on an English language literature search using MEDLINE from 1966 and CANCERLIT from 1983 to Jan. 1, 1997. Search terms included the following: breast neoplasms, segmental mastectomy, lumpectomy, breast conservation, radiotherapy, irradiation, clinical trials, research design, practice guidelines and meta-analysis. Bibliographies from recent published reviews were scanned and relevant articles retrieved.

As the initial draft of this guideline was prepared by the same authors as the Ontario document, the contents and conclusions of the 2 documents are in substantial agreement and the wording of some sections is similar.1

**Recommendations (including evidence and rationale)**

**The role of radiation therapy after BCS**

- Women who undergo BCS should be advised to have postoperative breast irradiation.

There is level I evidence that breast irradiation after BCS reduces the incidence of local recurrence, providing a survival rate equivalent to that of mastectomy.2–10 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 randomized 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.2–4 There was no difference in survival between the 3 treatment groups at a median follow-up of 12.5 years.4 However, for all patients who received a lumpectomy plus local breast irradiation of 50 Gy over 5 weeks to the whole breast, the rate of local recurrence in the breast was substantially lower at 10% than that of patients who were treated only with lumpectomy at 35% (p < 0.001).4 For node-negative patients treated by lumpectomy, local recurrence with adjuvant radiotherapy was 12% versus 32% for those who received no adjuvant radiotherapy; for node-positive patients, who also received chemotherapy, local recurrence for those with adjuvant radiotherapy was 5% versus 41% for those without adjuvant radiotherapy (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 followed up after treatment. After sector resection, women received either breast irradiation (54 Gy in 5 weeks to the whole breast) or no breast irradiation.1–6 At 5 years’ follow-up, the local recurrence rate was lower in those who received irradiation (2.3%) than in those who did not (18.4%, p < 0.0001).4 There was no difference in survival between the 2 treatment groups (level I evidence).

In a Canadian study, 837 node-negative patients were randomized after lumpectomy 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).7 The rate of local breast recurrence at 7.6 years was 35% for the no-radiation group compared with 11% for the radiation group (p < 0.001).8 There was no difference in overall survival (level I evidence).

In an Italian trial of 579 women with both node-negative and node-positive tumours less than 2.5 cm in diameter, patients were randomized to undergo quadrantectomy followed by breast irradiation (50 Gy in 20 to 25 fractions to the whole breast plus a boost to the tumour bed of 10 Gy in 5 fractions), or to quadrantectomy without radiotherapy.9 The rate of local recurrence in the irradiated patients at a median follow-up of 39 months was 0.3% and in the control group was 8.8% (p = 0.001). There was no difference in overall survival (level I evidence).

In another trial, in Scotland, 585 women with primary breast cancers 4 cm or less in diameter were randomized, 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 radiotherapy.10 At 6 years there was no difference in overall survival, but local regional recurrence rates were significantly lower in the irradiated group, at 5.8% compared with the non-irradiated group, at 24.5% (p = 0.05) (level I evidence).
The results of the meta-analysis of the Early Breast Cancer Trialists is consistent with the findings of these 5 studies. The reduction in risk of local recurrence after radiotherapy was 75% with no significant impact on survival (level I evidence).11

In most of these trials, local relapse was followed by mastectomy despite a policy of re-excision followed by breast irradiation for local relapse in patients treated by lumpectomy alone:10 the Swedish study1 reported an overall mastectomy rate for local recurrence of over 80%, the Canadian trial9 reported a mastectomy rate of approximately 50% and the Italian study7 reported a mastectomy rate of 40%.

- Omission of radiotherapy after BCS almost always increases the risk of local recurrence.

Are there any situations which confer so low a risk of recurrence that irradiation can safely be omitted? The probability of local recurrence without radiotherapy is less when tumours are small (less than 2 cm in diameter) and when women are older than 50 years of age (level I evidence). However, omission of irradiation after BCS increases the risk of local recurrence significantly, even in these cases. The Canadian study that evaluated the role of breast irradiation after lumpectomy in node-negative patients found that those aged 50 years and older who had tumours 2 cm or less in diameter were possibly a low-risk group.1 However, the rate of local relapse for such women treated by lumpectomy alone was 22% at 7.6 years median follow-up.4 Similarly, in further follow-up of patients in the NSABP B-06 study, it was noted that although tumour size predicted local recurrence in the breast, the risk of recurrence after BCS for node-negative patients with tumours 1 cm or less in diameter was still 25% at 8.5 years (level III evidence).12

Patients in whom more extensive resection is undertaken are also at somewhat lower risk (level III evidence). In the Uppsala-Örebro Breast Cancer Study Group trial, eligibility was limited to node-negative patients with tumours 2 cm or less in diameter who were treated with a sector resection, which was felt to be a more extensive surgical procedure than BCS alone, and comparable to quadrantectomy. The actuarial local breast recurrence rate for patients treated with surgery alone was 7.6% at 3 years and 18.4% at 5 years.14 In the Milan study in which patients were treated with a quadrantectomy, the rate of local recurrence after surgery alone was 8.8% after 3.25 years. However, this lower rate appears to have been at the expense of a worse cosmetic outcome.15

Investigators have evaluated the role of chemotherapy without irradiation in preventing local recurrence in the breast after BCS. An Ontario study of node-positive patients 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 treatment. There were fewer local recurrences after the longer, 36-week systemic treatment (23%) with the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) plus vincristine and prednisone (CMFVP) compared with the local recurrence rate after 12 weeks of treatment (39%, p = 0.02). However, these recurrence rates were not sufficiently reduced to justify replacement of breast irradiation with chemotherapy.14

In another trial from the Scottish Cancer Trials Breast group, 585 women who underwent BCS were randomized to receive or not receive radiotherapy. All received systemic therapy, either tamoxifen or intravenously administered CMF according to the estrogen receptor status of the tumour. At a median of 5.7 years, the local relapse rate for those receiving radiotherapy was 5.8% compared with 24.5% for those who did not receive radiotherapy (level I evidence).10 Thus, unless a woman is participating in a therapeutic trial that is specifically evaluating this issue, it is recommended that radiotherapy be given to all patients after BCS (level III evidence).

Contraindications to breast irradiation

- Contraindications to breast irradiation include pregnancy, previous breast irradiation (including mantle radiation for Hodgkin’s disease) and inability to lie flat or to abduct the arm. Scleroderma and systemic lupus erythematosus constitute 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 irradiation of the thorax involving a high dosage precludes further radiotherapy. Increased acute and late radiation effects have been reported in patients with pre-existing collagen vascular disease, including scleroderma and systemic lupus erythematosus.15,16 Although a study of 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 with “collagen vascular disease” had rheumatoid arthritis, which is not considered a contraindication to irradiation.17 Thus, based on present evidence, scleroderma and systemic lupus erythematosus should be considered relative contraindications to radiotherapy (level III evidence). When these conditions are present, women should be made aware that the risk of local recurrence is increased without radiotherapy, and that this can be avoided by mastectomy.

Radiation techniques

- The commonest fractionation schedule used in Canada is 50 Gy in 25 fractions to the whole breast without a boost when excision margins are clear of disease. Alternative schedules that may be used range from 40 Gy in 16 fractions to the whole breast, with or without a boost, to 45 Gy in 25 fractions with a boost of 16 Gy in 8 fractions to the primary site. The role of boost irradiation to the primary site is unclear. Irradiation of the whole breast rather than partial irradiation is recommended.

In planning therapy, the 2 main considerations are con-
trolling local recurrence and obtaining a satisfactory cosmetic outcome. There are as yet no completed randomized clinical trials comparing different fractionation schedules for breast irradiation after BCS. Thus, the conclusions that follow are based on relatively insecure evidence.

In the 5 randomized trials of breast irradiation versus no breast irradiation after lumpectomy, already discussed, no studies used the same radiation fractionation schedule.\(^\text{2, 10, 18}\) However, in patients with comparable stages of breast cancer and similar length of follow-up, the rates of local recurrence were similar (level III evidence).

Six trials have compared BCS followed by radiotherapy using modern techniques to mastectomy alone.\(^\text{4, 19–21}\) Although different fractionation schedules were used in each trial, local recurrence rates were comparable for patients who had comparable treatment schedules and length of follow-up.

Based on a retrospective study, van Limbergen and colleagues found that local recurrence was reduced as the dose of radiotherapy increased, but the cosmetic outcome worsened.\(^\text{14, 21}\) However, others have not found a dose-response relationship.\(^\text{20}\)

The optimal fractionation schedule for breast irradiation has not been established.

The most common fractionation schedule used in Canada is 50 Gy in 25 fractions to the whole breast without a boost when the margins of surgical excision are clear of disease (the same schedule used in the NSABP study).\(^\text{2}\) Two schedules most widely used in a review of patients eligible for (but not entered in) the Canadian trial were 50 Gy in 25 fractions and 40 Gy in 16 fractions plus a boost of 12.5 Gy in 5 fractions to the primary site (the same schedule used in the Canadian study).\(^\text{2}\) Other fractionation schedules have also been used routinely in some centres in Canada. Examples include: 40 Gy in 15 fractions or 44 Gy in 16 fractions to the whole breast without a boost; or 45 Gy in 25 fractions with a boost of 16 Gy in 8 fractions to the primary site. Indirect comparisons between studies (a highly unreliable source of evidence) suggest that local recurrence, cosmetic outcome and survival with these schedules are roughly comparable. Thus, within this range of fractionation factors, such as resource use and patients’ lifestyle needs should influence the choice of schedule, with some patients preferring the shorter, less disruptive courses of irradiation.\(^\text{29}\)

Any beneficial effect of boost irradiation to the primary site following whole breast irradiation is as yet unproven.

Randomized trials evaluating the role of boost irradiation are ongoing. However, indirect comparisons between trials suggest that the risk reduction for local recurrence in patients with clear margins after BCS is similar whether a boost is used or not (level III evidence).\(^\text{2, 19, 29}\) Also, evidence from retrospective cohort studies suggests that for patients with microscopically clear margins treated with 50 Gy or more irradiation to the whole breast, a supplementary boost does not decrease local recurrence and may worsen cosmetic outcome (level III evidence).\(^\text{20–21}\)

Controversy exists regarding further management when the pathologist reports microscopic involvement of the resection margins with invasive cancer or DCIS.\(^\text{22–24}\) In this situation, patients are at increased risk of local recurrence, and reexcision or mastectomy should be considered, especially if there is more than focal involvement (level III evidence).\(^\text{27}\) Patients should be informed when margins are involved, and if surgery is declined, it is normal practice in North America to recommend boost irradiation (level IV evidence).\(^\text{35}\) However, its efficacy in this situation remains unclear.

**Whole breast irradiation results in lower recurrence rates than partial breast irradiation (level I evidence).**

In a trial comparing whole versus partial breast irradiation, 708 patients were randomized following BCS to receive whole or partial breast irradiation.\(^\text{28}\) At a median follow-up of 7 years, local recurrence rates were 11% for the whole breast irradiation group and 19.6% for the partial breast irradiation group (\(p < 0.008\)). There was no difference in survival.

**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 radiotherapy.**

The data that are available regarding these issues constitute level III evidence based on case series of patients who were treated mostly by irradiation of the breast, supraclavicular and axillary regions. Thus, the data tend to overestimate the complications that can be expected after simple breast irradiation, which is the treatment usually given following BCS for early cancer.

**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 after radiotherapy. Both symptoms usually resolve completely within 3 to 6 months.

**Mild and moderate long-term effects of irradiation are relatively rare (level III evidence).**\(^\text{37–40}\)

During the first 2 years after surgery and radiotherapy, patients may experience intermittent pain in the breast, the cause of which is unclear. It is usually self-limiting and seldom severe.\(^\text{41}\) The results of a recent British Columbia study suggest that the following effects may be experienced 5 years after BCS followed by irradiation of the breast alone: 18% of patients may experience mild discomfort in the breast and 2% may feel moderate or severe discomfort, 6% may have mild...
breast erythema, 3% may have mild breast edema, 1.6% may have moderate or severe breast induration and 13% may have mild and 0.8% moderate or severe telangiectasia over the breast area. The discomfort, erythema, edema and induration were related to both surgery and radiotherapy.41

**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.40-42 Evaluation of cosmetic outcome has primarily been based on physician evaluation in case series.31,40,43,44 A satisfactory result is reported in 80% to 95% of patients.45 Other studies have failed to show any connection between irradiation and contralateral breast cancer (level III evidence). However, techniques should be used that minimize exposure to the opposite breast, especially in younger women (level IV evidence).

**Severe long-term ill effects of irradiation are rare (level III evidence).**

Based on an overview of 4 substantial follow-up series, the following complications can be expected after irradiation of both breast and nodal areas: pneumonitis in 0.7% to 7.0%, pericarditis in 0% to 0.3%, rib fracture in 1.1% to 1.5%, brachial plexopathy in 0% to 1.8% and significant arm edema (in the absence of axillary dissection) in 1%.41 In an institutional study of 1624 patients treated at the Joint Center for Radiation Therapy from 1968 to 1985, severe effects consisted of tissue necrosis in 1.8%, brachial plexopathy in 1.8% (in those receiving supraclavicular irradiation), rib fracture in 1.8%, pericarditis in 0.4% and pneumonitis in 0.2% (level III evidence).46,47 However, it should be noted that many of these complications were associated with techniques involving regional irradiation and large total doses and fraction sizes that are no longer in use.

Data from the Swedish cancer registry indicate a significantly higher death rate due to myocardial infarction in patients with left-sided tumours than patients with right-sided tumours.60 A review of the complications of radiotherapy after BCS concludes that in patients with left-sided breast cancer who receive irradiation of internal mammary nodes, there is evidence to suggest a possible increase in rates of myocardial infarction and late cardiovascular deaths. The reviewers point out that although the irradiation techniques employed would not be acceptable today, there is sufficient evidence to indicate that caution should observed when irradiation may involve the anterior aspect of the heart.41 In the Canadian randomized study, when the breast alone was irradiated there was no evidence of an increased cardiovascular death rate after 7.6 years.4

**There is no evidence of any significant increase in the risk of malignant disease resulting from breast irradiation after BCS (level III evidence).**

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

**Breast cancer**

In a case-controlled study of women under 43 years of age, a marginally significant elevation of risk of contralateral breast cancer was found after radiation after mastectomy.49 However, for most patients other relevant risk factors such as family history and histologic subtype were not reported.49 Other studies have failed to show any connection between irradiation and contralateral breast cancer (level III evidence).50-52 Thus, at present, there is no convincing evidence to support any such association.11 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 radiotherapy have involved orthovoltage therapy and regional as well as local breast irradiation.4 A review of the evidence in 1992 concluded that possibly 1 to 2 soft-tissue sarcomas per 1000 patients per decade of follow-up might be expected to result from radiotherapy.41

**Leukemia**

There is no convincing evidence of increased risk of leukemia associated with radiotherapy to the breast. In a case-controlled study of 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 radiotherapy, which increased with increasing dosage. However, after the exclusion of patients treated with alkylating agents, the relative risk of leukemia attributable to radiotherapy was not statistically significant.33

Thus, although a theoretic risk remains, there is no convincing evidence of a clinically significant association between breast irradiation for early breast cancer and subsequent malignant disease.

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

A review of the extensive level III evidence available indicates that BCS followed by breast irradiation, within the limits described above, is associated with very few significant complications.41 The frequency and severity of complications and poor cosmetic results increases with the use of unusual dosages or dosage schedules, or when regional node irradiation...
The optimal sequencing of chemotherapy and irradiation is used as well. Suboptimal techniques that result in unacceptable dose heterogeneity may also contribute to adverse cosmetic outcomes.25

**The time interval between surgery and radiotherapy**

- It is recommended that local breast irradiation should be started as soon as possible after surgery and not later than 12 weeks after, except for patients in whom radiotherapy is preceded by chemotherapy. However, the optimal interval between BCS and the start of irradiation has not been defined.

The timing of radiotherapy has been studied in a cohort study involving 436 patients. Patients who began radiotherapy more than 7 weeks after BCS appeared to be at greater risk of recurrence (14%) than patients receiving treatment earlier (5%).14 However, the interval between radiotherapy and surgery was not significant when other relevant factors were considered in multivariate analysis (level III evidence).

Likewise, in a study of 653 node-negative patients 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 radiotherapy (level III evidence).65

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 (level IV evidence), but in a survey reported in 1995, only 55% of patients received radiotherapy within this interval.66 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 (level V evidence).

**The sequencing of chemotherapy and radiotherapy**

- The optimal sequencing of chemotherapy and irradiation is not clearly defined for patients who are also candidates for chemotherapy. Most centres favour the administration of chemotherapy before radiotherapy. Selected chemotherapy regimens are sometimes used concurrently with radiotherapy. There is no evidence that this results in better outcome, and there is an increased chance of toxic effects, especially for anthracycline-containing regimens.

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

In a trial involving 250 patients randomly assigned to receive radiotherapy before or after chemotherapy, those who underwent radiotherapy before chemotherapy showed a higher distant recurrence rate (36%) at 5 years than those who had chemotherapy followed by radiotherapy (25%) \((p = 0.05)\). However, the radiotherapy-first group had a lower local recurrence rate (5%) than the chemotherapy-first group (14%) \((p = 0.07)\), and the overall survival rates were comparable (level II evidence).67 However, the interpretation of these findings is confounded by the observation that some patients in the radiotherapy-first group received a lower mean dose of chemotherapy agents (level II evidence). The timing of radiotherapy has been considered in other studies with inconsistent results (level III evidence).68-71

In several trials designed to evaluate adjuvant chemotherapy regimens after BCS, radiotherapy was delayed until chemotherapy was completed without any apparent increase in local recurrence.69-71

Apart from questions of survival and local recurrence, several case series have shown that when chemotherapy and radiotherapy are given concurrently, the potential for increased acute and late adverse effects of radiotherapy, including a worse cosmetic outcome, is increased.13 This is especially so when anthracycline-based regimens are used (level III evidence).68-69

**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 often is 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 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 patients should be given the chance to participate.

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