

Cancer Care Ontario Practice Guidelines Initiative

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Cancer Care Ontario & Ontario Ministry of Health and Long-Term Care



Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast Conserving Surgery

Practice Guideline Report #1-2

ORIGINAL GUIDELINE: March 11, 1997

UPDATE: January 2002

The Breast Cancer Disease Site Group is rewriting this practice guideline report. The revised guideline report will incorporate all new evidence that has become available since the guideline was completed in 1997. The new evidence under review is noted below (labelled NEW), and is identified in the update sections of the full report. The current guideline recommendations remain in effect.

SUMMARY

Guideline Questions

- Should breast irradiation be given to women with early stage breast cancer (stage I and II) following breast-conserving surgery (lumpectomy with clear resection margins and axillary dissection)?
- Is there an optimal schedule for breast irradiation?
- What is a reasonable interval between definitive surgery and commencing radiation?
- Are there patients who can be spared breast irradiation after lumpectomy?

Target Population

These recommendations apply to adult patients with early-stage (stages I and II) invasive breast cancer who have had breast-conserving surgery.

Recommendations

- Women with early stage (stages I and II) breast cancer who have undergone breast-conserving surgery (defined as excision of the tumour with clear resection margins) should be offered postoperative breast irradiation.
- The optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. Outside of a clinical trial, two commonly used fractionation schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions. Shorter schedules (e.g., 40 or 44 Gy in 16 fractions) have also been used routinely in some centres. The enrolment of patients in ongoing clinical trials is encouraged.

- Women who have undergone breast-conserving surgery should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery.
- For women who are candidates for chemotherapy, the optimal sequencing of chemotherapy and radiotherapy is unknown. It is reasonable to start radiotherapy after the completion of chemotherapy, or concurrently if anthracycline-containing regimens are not used.

Methods

MEDLINE and CANCELIT searches were done for the years 1966-1999 using the terms segmental mastectomy, lumpectomy, breast conservation, clinical trials, random allocation, double-blind method, guideline, meta-analysis and review. The bibliographies of articles identified by the searches, recent reviews, relevant articles and personal files were reviewed.

Evidence was selected and reviewed by members of the cancer Care Ontario Practice Guideline Initiative (CCOPGI) Breast Cancer Disease site Group (DSG). This practice guideline has been reviewed and approved by the Breast cancer DSG, which is comprised of surgeons, medical oncologists, epidemiologists, a pathologist and a medical sociologist, and a community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

NEW

Entries to MEDLINE (through to December 2001), the Cochrane Library (through to Issue 4, 2001) and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society of Radiation Oncology have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in January 2002. New evidence is currently under review by the Breast Cancer Disease Site Group.

Key Evidence

- Breast irradiation versus no breast irradiation: There were four randomized controlled trials and one meta-analysis comparing breast irradiation versus no breast irradiation following breast-conserving surgery. Results indicate a significant decrease in local recurrence rates for patients receiving radiotherapy. In the four trials with a median follow-up of five years or longer, the relative risk reduction with breast irradiation ranged from 73 to 89%. The absolute differences ranged from 16% ($p < 0.001$) to 29% ($p < 0.0001$). Despite the effect on local recurrence, no difference in survival was detected in any of the five trials. Most of the patients with breast recurrence in these trials underwent mastectomy.
- Fractionation schedules: Four randomized trials and two retrospective studies were identified. The optimal fractionation schedule cannot be established from the available data.
- Time to radiation therapy: There were no randomized trials comparing different time intervals between surgery and commencement of radiotherapy. Data from the four randomized trials comparing radiation versus no radiation following breast-conserving surgery, six randomized trials comparing lumpectomy plus radiation versus mastectomy, two large cohort studies, an ongoing randomized trial of chemotherapy followed by radiotherapy versus radiotherapy followed by chemotherapy, and five cohort studies examining the effect

of the sequencing of chemotherapy and radiotherapy were reviewed. Based on this evidence, the maximum interval between surgery and commencement of radiation therapy was defined as 12 weeks.

January 2002:

- In April 1997, additional evidence from: two randomized trials examining the efficacy of breast irradiation following breast-conserving surgery and from a meta-analysis and randomized trial examining its adverse effects was identified and reviewed by the Breast Cancer DSG. No changes were made to the recommendations at that time.
- In September 1999, additional evidence from: a practice guideline, a randomized trial of boost radiation, updated results of a randomized trial described in the original guideline report, and data on arm symptoms from a randomized trial of breast-conserving surgery with and without radiotherapy were identified and reviewed by the Breast Cancer DSG. No changes were made to the recommendations in 1999.
- The Breast Cancer Disease Site Group is reviewing new evidence from: a randomized trial of lumpectomy with or without postoperative radiotherapy for patients with favourable prognostic factors, three additional randomized trials of boost radiation, a randomized trial comparing two fractionation schedules, an updated meta-analysis of radiotherapy versus control, two reports of quality-of-life data from randomized trials, and three randomized trials of tamoxifen versus radiotherapy plus tamoxifen.

Prepared by the Breast Cancer Disease Site Group

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PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, community representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:

<http://www.cancercare.on.ca/ccopgi/>

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FULL REPORT

Original guideline information and new information that has emerged from review and updating activities is labelled ORIGINAL and UPDATE, respectively.

I. QUESTION

Should breast irradiation be given to women with early stage breast cancer (stage I and II) following breast conservation surgery (lumpectomy with clear resection margins and axillary dissection)? Is there an optimal schedule for breast irradiation? What is a reasonable interval between definitive surgery and commencing radiation? Are there patients who can be spared breast irradiation after lumpectomy?

II. CHOICE OF TOPIC AND RATIONALE

Approximately 80% of women who present with breast cancer will have early stage disease (Stages I and II - Appendix 1). It has been demonstrated through randomized trials that lumpectomy is equivalent, in terms of survival, to more radical surgery, for example, mastectomy¹. In view of the increasing use of lumpectomy and the number of well-executed clinical trials evaluating the role of breast irradiation following this treatment, the Provincial Breast Disease Site Group felt that a practice guideline was warranted.

III. METHODS

Guideline Development

This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle by Browman et al.² Evidence was selected and reviewed by members of the CCOPGI's Breast Cancer Disease Site Group (Breast Cancer DSG) and methodologists. The guideline is a convenient and up-to-date source of the best available evidence on the use of breast irradiation in women with early stage breast cancer following lumpectomy, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. It is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Guideline History

This practice guideline report was originally completed on March 11, 1997 and published in *Cancer Prevention and Control* 1997;1(3):228-40. The guideline was reviewed monthly in 1997, 1998, 1999, and quarterly beginning in 2000 with the most recent update being January 2002. This guideline is in the process of being rewritten. The original guideline report and new

¹ For further information about the efficacy of lumpectomy in the treatment of early stage breast cancer, please refer to the Ontario Cancer Treatment Practice Guidelines Initiative's Practice Guideline: Surgical Management of Early Stage Breast Cancer (Stage I and II), PG#1-1.

² Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

information that has emerged from review and updating activities is labelled ORIGINAL and UPDATE, respectively, in this report.

Literature Search Strategy

Original: March 1997

MEDLINE and CANCERLIT searches were completed for the years 1966 to January, 1996. Search terms included: breast neoplasms, segmental mastectomy, lumpectomy, breast conservation, radiotherapy, irradiation, clinical trials, research design, practice guidelines and meta-analysis. Bibliographies from recent published reviews were reviewed and relevant articles were retrieved.

Update: January 2002

The literature search was revised to combine disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s]), treatment-specific terms (mastectomy, segmental, lumpectomy, quadrantectomy, conserving, conservation, radiation, irradiation, radiotherapy), and design-specific terms (meta-analysis, randomized controlled trial[s]).

The literature was searched using MEDLINE (through December 2001), the Cochrane Library (Issue 4, 2001), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the European Society for Medical Oncology.

Inclusion Criteria

Original: March 1997

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria: Randomized controlled trials comparing breast-conserving surgery plus or minus breast irradiation, which reported local recurrence rates and survival, or case series which reported on morbidity.

Update: April 2001

Articles (abstracts or full reports) were selected if they were meta-analyses or randomized controlled trials comparing irradiation versus no irradiation after breast conservation therapy. Outcomes of interest included overall or disease-free survival, local recurrence, distant recurrence, quality of life, and adverse effects. Randomized trials investigating fractionation schedules, boost irradiation, time to radiation therapy and adverse events were also eligible for inclusion.

Synthesizing the Evidence

Data were not pooled for this practice guideline report.

IV. RESULTS

Literature Search Results

Original: March 1997

There are four randomized controlled trials and one meta-analysis comparing breast irradiation versus no-breast irradiation following breast conserving surgery. Evidence from six randomized trials comparing breast conserving surgery plus breast irradiation with mastectomy and several retrospective studies are also used.

Update: January 2002

New evidence in the April 1997 update included: two randomized trials examining the efficacy of breast irradiation following breast conserving surgery and from a meta-analysis and randomized trial examining its adverse effects.

New evidence in the September 1999 update included: a practice guideline, a randomized trial of boost radiation, updated results of a randomized trial described in the original report, an data

on arm symptoms from a randomized trial of breast-conserving surgery with and without radiotherapy.

The Breast Cancer Disease Site Group is reviewing evidence collected between September 1999 and December 2001 from:

- a randomized trial of lumpectomy with or without postoperative radiotherapy for patients with favourable prognostic factors (13u),
- three additional randomized trials of boost radiation (14u-16u),
- a randomized trial comparing two fractionation schedules (17u),
- an updated meta-analysis of radiotherapy versus control (18u),
- two reports of quality-of-life data from randomized trials (19u,20u),
- three randomized trials of tamoxifen versus radiotherapy plus tamoxifen (21u-23u).

Trials Evaluating Breast Irradiation Following Breast Conserving Surgery

Original: March 1997

There have been four randomized trials evaluating breast irradiation following breast conserving surgery. In the NSABP B-06 trial (1,2,3), 2,105 women with node-negative or node-positive breast cancer and tumours ≤ 4 cm were randomized to one of three treatment arms: i) modified radical mastectomy, ii) lumpectomy plus axillary dissection followed by local breast irradiation, or iii) lumpectomy and axillary dissection alone. At a median follow-up of 12.5 years, no difference was detected in terms of overall survival between the three treatment groups in the study (3). In patients who received local breast irradiation of 5000 cGy over five weeks to the whole breast (2), there was substantial reduction in local breast recurrence compared to patients who were treated only with lumpectomy (10% versus 35%, $p < 0.001$). For node-negative patients treated by lumpectomy, local recurrence with or without adjuvant radiotherapy was 12% and 32% respectively; and for node-positive patients, it was 5% and 41% respectively (node-positive patients also received adjuvant chemotherapy).

The Uppsala-Örebro Breast Cancer Study Group (4,5) recently reported the update of a trial in which 381 women with node-negative breast cancer, primary tumours ≤ 2 cm were randomized after sector resection to receive either breast irradiation (5400 cGy in five weeks to the whole breast) or no breast irradiation. At five years follow-up (5), there was a statistically significant difference in local breast recurrence between the radiation versus the no-radiation groups (2.3% versus 18.4% respectively, $p < 0.0001$). There was no difference in survival between the two treatment groups.

In the Ontario Clinical Oncology Group (OCOG) trial (6), 837 node-negative patients who had undergone lumpectomy were randomized to receive breast irradiation (4000 cGy in 16 fractions over three weeks to the whole breast plus a local boost of 1250 cGy in five fractions over one week to the primary site) or no breast irradiation. At a median follow-up of 66 months (7), the cumulative rate of local breast recurrence at five years was significantly reduced for the radiation group compared to the no-treatment group (8% versus 30% respectively, $p < 0.0001$). No difference was detected in overall survival.

In the most recently published Milan trial (8), 567 women with node-positive breast cancer with primary tumours < 2.5 cm in diameter were randomized to quadrantectomy followed by breast irradiation (5000 cGy in 25 fractions to the whole breast plus a boost to the tumour bed of 1000 cGy in five fractions) or a quadrantectomy without radiotherapy. At a median follow-up of 39 months, there was a statistically significant decrease in local breast recurrence in the radiation group as compared to the no-radiation group (0.3% versus 8.8% respectively, $p = 0.001$). Overall survival was similar between the two treatment groups.

Local relapse often resulted in mastectomy in most of these trials despite a policy of re-excision followed by breast irradiation for local relapse in patients treated by lumpectomy alone. The Swedish study (5) reported an overall mastectomy rate for local recurrence of 70%, the

OCOG trial (6) reported a mastectomy rate of approximately 50%, and the Milan study (8) reported a mastectomy rate of 40%.

A recent meta analysis of all published and unpublished randomized trials initiated before 1985 supports the findings of the four studies discussed above (9). Odds reduction for local relapse was 0.75. No significant impact on survival was demonstrated.

Acute and late radiation complications, poor cosmetic outcome and carcinogenicity have all been studied as potential adverse effects of breast irradiation. Unfortunately, in the four randomized trials reviewed, rates of acute and late toxicity or quality of life have not been formally reported. The data that is available to address these issues comes from case series. One of the largest is an institutional study of 1,624 patients treated at the Joint Center for Radiation Therapy from 1968 to 1985 (10,11). The authors report a very low incidence of severe toxicity consisting of tissue necrosis (0.2%), rib fracture (0.5%), pericarditis (0.4%) and pneumonitis (0.2%). Of the complications that were reported, many were associated with techniques involving large total doses and fraction sizes that are not in current use. Moderate toxicity consisting of breast edema, fibrosis and pain or discomfort has been noted in 5-9% of patients treated with breast irradiation post-lumpectomy in other case series (12-14). Many of these late effects are thought to impinge on cosmetic outcome, which primarily has been physician evaluated in case series (15-17). In a subset of patients treated in the Swedish randomized trial (18), patient-evaluated cosmetic outcome after lumpectomy alone versus lumpectomy plus radiation was equivalent with 80% of patients reporting a good or excellent cosmetic outcome.

The results from randomized trials have demonstrated no increased risk of contralateral breast cancer in patients receiving radiation when compared to mastectomy. In a large case control study (19), Boice et al noted a small but marginally significant elevated risk of contralateral breast cancer following radiation post-mastectomy. This risk was primarily seen in women under the age of 45 and was not observed in older women. Unfortunately, this study lacked sufficient information on other important risk factors for contralateral breast cancer, such as family history and lobular histologic subtype. Three other large case control studies (20-22) have failed to show a connection between radiation and contralateral breast cancer. Thus, this association remains uncertain. An additional concern is the potential for radiation-induced sarcomas either in bone or soft tissue. The Joint Center reported (11) three cases of sarcoma (incidence of 0.18%), but all cases involved patients with regional as well as local breast irradiation.

Increased acute and late effects of radiation have been reported in several case reports and series of patients with pre-existing collagen vascular disease, including scleroderma and lupus (23,24). A recent study of 122 patients using a matched cohort design suggested no statistical difference between patients with collagen vascular disease and normal controls for acute or late complications (25). Contraindications to breast irradiation are discussed in PG#1-1, Surgical Management of Early Stage Invasive Breast Cancer and include previous breast irradiation (including mantle radiation for Hodgkin's Disease), pregnancy, severe heart or lung disease, scleroderma and lupus.

Update: January 2002

This update section summarizes the evidence collected between completion of the guideline in March 1997 and September 1999.

Additional Randomized Trial

The literature search in April 1997 found one additional randomized controlled trial of breast irradiation. In a trial by the Scottish Cancer Trials Breast Group (1u), 585 women with node-negative and -positive breast cancer with primary tumours four cm in size or less were randomly assigned, after lumpectomy and systemic therapy, to receive 50 Gy in 20 to 25 fractions to the breast with a boost to the primary site (20 to 30 Gy by iridium implant or 10 to 15 Gy by external

beam irradiation) or no radiotherapy. At a median follow-up time of 5.7 years, the local regional recurrence rate was significantly lower for those receiving radiation therapy (5.8% versus 24.5%, $p < 0.05$); there was no difference in overall survival.

All patients received systemic therapy, either tamoxifen or intravenous CMF (cyclophosphamide, methotrexate, fluorouracil), according to the estrogen-receptor status of the tumour. Investigators were unable to identify a subgroup of patients that did not benefit from adjuvant radiation therapy in this setting.

Updated Results of Randomized Trials

Updated results from the Ontario Clinical Oncology Group (OCOG) trial of breast irradiation following lumpectomy have been published since the practice guideline was released (2u). In this trial, 837 node-negative patients who had undergone lumpectomy were randomly allocated to receive breast irradiation (40 Gy in 16 fractions over three weeks to the whole breast plus a local boost of 12.5 Gy in five fractions over one week to the primary site) or no breast irradiation. At a median follow-up of 7.6 years, the cumulative rate of local breast recurrence at five years was significantly lower in the radiation group than in the control group (11% versus 35% respectively, $p < 0.001$). No difference was detected in overall survival.

The Uppsala-Orebro Breast Cancer Study Group has published an update on a trial in which 381 women with node-negative breast cancer and tumours < 2 cm in size were randomized to receive postoperative radiotherapy to the breast or no further treatment after sector resection plus axillary dissection (11u). After 10 years of follow-up, the local recurrence rate was 8.5% in the irradiated group and 24.0% in the control group ($p = 0.0001$). The overall survival rate was 78% in both groups.

Practice Guideline from Another Guideline Development Group

In July 1997, the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer recommended that women who undergo breast-conserving surgery should be advised to have postoperative radiotherapy (9u). This recommendation was based on evidence from the five randomized controlled trials and one individual-patient-data meta-analysis that were used as the basis for the Cancer Care Ontario guideline. Recommendations on fractionation schedule and the timing of radiotherapy were consistent with the Ontario guideline. Development of the guideline report included feedback from reviewers outside of the writing group and steering committee; breast cancer survivors were included among the reviewers.

Fractionation Schedules for Breast Irradiation Post-lumpectomy

Original: March 1997

The literature was examined from several perspectives: direct comparisons of different fractionation schedules in a randomized clinical trial; indirect comparisons or between study comparisons of different fractionation schedules evaluated in randomized trials; and retrospective cohort studies analyzing dose response relationships.

Four randomized clinical trials comparing different fractionation schedules for breast irradiation post-lumpectomy were identified (26-29). One randomized trial comparing 4500 cGy in 25 fractions over five weeks versus 2300 cGy in six fractions over 2 to 5 weeks has been incompletely reported, and is not generalizable as it included patients treated with radiotherapy post-mastectomy or as primary treatment alone (26). Three other trials were identified, but they either are ongoing or have not been formally reported. The Institute of Cancer Research in Sutton, England is comparing three fractionation schedules post-lumpectomy: 5000 cGy in 25 fractions over five weeks; 4290 cGy in 13 fractions over three weeks; and 3900 cGy in 13 fractions over three weeks (27). The West Midland Cancer Research Study Campaign is comparing 4000 cGy in 15 fractions over three weeks versus 5000 cGy in 25 fractions over five

weeks with a supplementary boost of 1500 cGy in five fractions over one week to the primary site given to patients in both arms (28). The Ontario Clinical Oncology Group is comparing a course of 5000 cGy in 25 fractions over five weeks versus 4250 cGy in 16 fractions over three weeks (29).

There have been four randomized trials (2,5,6,8) comparing breast irradiation with no breast irradiation for patients who have undergone lumpectomy (Table 1). In all studies, a different radiation fractionation schedule was employed for breast irradiation post-lumpectomy. The rates of local breast recurrence following radiotherapy in comparably staged patients with similar follow-up are equivalent. In addition, the relative risk reduction for local recurrence is also similar for the different fractionation schedules used, suggesting comparable efficacy.

There have been six trials (1-3,30-34) in which breast conserving surgery plus radiation using modern techniques has been compared with modified radical mastectomy (Table 2). In all these studies, a different fractionation schedule was used, and the rates of local breast recurrence in similar patients with similar follow-up are equivalent. Unfortunately, information regarding rate of toxicity, cosmetic outcome and quality of life have not been well reported in the majority of these trials.

There also have been several retrospective studies of breast irradiation following lumpectomy. A study by Van Limbergen and colleagues (35) concluded that there was a significant gain in local control with increasing radiotherapy dose. At the same time, higher doses led to worse cosmetic results. In another study by Bataini and colleagues (36), no significant dose response relationship could be documented.

Not surprisingly, given the lack of evidence available, surveys of radiotherapy practice for the treatment of breast cancer have shown wide variability in the number of different fractionation schedules used to treat women post-lumpectomy (37-40). In an Ontario survey of 550 patients who were eligible but who did not participate in the OCOG randomized clinical trial evaluating the use of breast irradiation and who were treated with radiotherapy, 48 different fractionation schedules were identified (40). The two most popular schedules were the schedule used in the OCOG trial (4000 cGy in 16 fractions to the whole breast plus a boost of 1250 cGy to the primary site over one week), and the schedule used in the NSABP trial (5000 cGy in 25 fractions to the whole breast in five weeks without a boost).

The role of boost irradiation to the primary site following whole breast irradiation is unclear. Only one randomized trial (the EORTC trial 108829) which is currently ongoing was identified. Patients with T₁₋₂, N₀₋₁ breast cancer treated by lumpectomy with clear resection margins followed by whole breast irradiation of 5000 cGy in 25 fractions are randomized to a boost to the primary site of 1500 cGy or no boost. Patients with involved margins are randomized to a boost of 1000 cGy or a boost of 2500 cGy. Indirect comparisons between randomized trials (3,5,6,8) suggest that the risk reduction for local recurrence is similar whether a boost is used or not (Table 1). Evidence from retrospective cohort studies suggests that for patients with microscopically clear margins treated with 5000 cGy whole breast irradiation, a supplementary boost does not increase local control and may worsen cosmetic outcome (16,41,42). For a discussion of the management of patients with positive resection margins following breast conserving surgery, please see the Ontario Cancer Treatment Practice Guidelines Initiative's Practice Guideline PG#1-1: *Surgical Management of Early Stage Breast Cancer (Stage I and II)*.

With regard to other technical considerations, such as the volume of breast that should be irradiated, we identified only one other randomized trial (43) where 708 post-lumpectomy patients were randomized to receive full breast irradiation (4000 cGy in 15 fractions over three weeks) or partial breast radiotherapy. At a median follow-up of seven years, there was a statistically significant difference in local relapse rates between whole breast radiotherapy and partial breast radiotherapy (11% versus 19.6% respectively, p<0.008). There was no statistically significant difference in survival between groups.

Update: January 2002

This update section summarizes the evidence collected between completion of the guideline in March 1997 and September 1999.

Between 1986 and 1992, 1024 women treated with breast-conserving surgery plus whole-breast irradiation of 50 Gy in 20 fractions over 5 weeks were randomized to receive a boost of 10 Gy to the tumour bed in four fractions over one week or no further treatment (10u). Ninety-eight percent of patients had free margins. At a median follow-up time of 3.3 years, there had been 10 local recurrences with boost irradiation and 20 without (log-rank $p=0.044$). There were 23 deaths in the boost group and 29 in the control group (log-rank $p=0.24$). Two years after treatment, 12.4% of the patients who received boost irradiation and 5.9% of the control patients experienced grade 1 or 2 telangiectasia ($p=0.003$); there were no cases of grade 3 telangiectasia.

Interval Between Definitive Surgery and Commencing Breast Irradiation**Original: March 1997**

No randomized controlled trials specifically comparing different time intervals between surgery and commencement of radiotherapy were identified. Thus, we chose three types of studies to review this topic: randomized trials comparing lumpectomy with or without radiotherapy, randomized trials comparing lumpectomy with mastectomy, and cohort studies in which patients received breast irradiation. In the four randomized trials comparing radiation with no radiation in patients who had undergone lumpectomy (2,5,6,8), information on the interval between surgery and commencing radiation was stated in three of these studies. In the NSABP B-06 study, patients with node-negative disease commenced radiation within six weeks of surgery and those with node-positive disease commenced RT within eight weeks of surgery (1-3). In the OCOG study (6), patients commenced radiation within 12 weeks of surgery and in the Milan study (8), radiation was commenced within six weeks of surgery. Results of these trials are summarized in Table 1.

The six studies in which lumpectomy plus radiotherapy was compared with modified radical mastectomy were also reviewed (see Table 2). The NSABP B-06 study is described above. In the Milan study (32), patients were treated with quadrantectomy and radiation was begun within 20 days. The rate of local breast recurrence was reported at 0.3%. In the Danish trial (31), patients were referred for radiation within four weeks of surgery, but information on the exact interval between surgery and the commencement of radiation was not presented. The local recurrence rate was 2.4%. In the EORTC study (30), radiation was commenced within six weeks of lumpectomy and local recurrence rate at six years was 9.3%. In the National Cancer Institute study (33), information on the interval between surgery and the onset of radiotherapy was not published.

Two large cohort studies were identified which addressed the issue of timing of radiotherapy. A study (44) from the Institut Gustave-Roussy of 436 patients suggested that patients treated with radiation beyond seven weeks following breast conservation surgery may have a greater risk of recurrence (14%) than patients treated within seven weeks (5%). However, when other risk factors for recurrence were considered in a multivariate analysis, the interval between radiation and surgery was no longer significant. The risk of local breast recurrence was recently examined in 653 node-negative patients treated at the Joint Center for Radiation Therapy from 1968 to 1985 (45). All patients received a dose of 6000 cGy or greater to the primary tumour site. No patients received adjuvant systemic therapy. The median length of follow-up in surviving patients was 100 months. Five-year rates of local breast recurrence were 13% for 282 patients treated with radiation within four weeks (measured from the day of their last surgical procedure on the breast), 7% for 306 patients treated in 5 to 8 weeks, and 2% among 54 patients treated within 9 to 12 weeks of surgery. A multivariate analysis showed no

difference in recurrence rates resulting from these different surgery to radiation therapy intervals while controlling for known and potentially confounding risk factors.

A relevant and separate issue regarding the interval between surgery and the commencement of breast irradiation is the integration of breast conserving surgery and radiation when patients are also treated with systemic adjuvant chemotherapy. There are several important issues to be considered including the ability to deliver adequate chemotherapy and radiotherapy, and the impact of combined treatment on local recurrence, complications and especially survival. The options for the sequencing of radiation and chemotherapy include the delivery of all chemotherapy prior to radiation, the delivery of radiation prior to chemotherapy (sequential regimens), the simultaneous institution of chemotherapy and radiation (concurrent regimens), or the initiation of radiotherapy in the midst of a chemotherapy program (sandwich regimen).

Recently, the Dana Farber Cancer Institute closed recruitment to a trial in which 250 patients were randomly allocated to receive radiation therapy followed by a 12-week course of chemotherapy (four cycles of Cyclophosphamide, Doxorubicin, Methotrexate, 5-Fluorouracil, Prednisone), or the same chemotherapy regimen followed by radiation therapy (46). The five-year actuarial results indicate that radiation preceding chemotherapy resulted in an increased rate of distant failure (36% versus 25%, $p=0.05$), a lower rate of local failure (5% versus 14%, $p=0.07$) but no difference in overall survival. Interpretation of this study is difficult in that non-standard chemotherapy was used and a proportion of patients received nodal radiation resulting in lower mean doses of chemotherapy received in the radiation first group. Nevertheless, the data suggest that chemotherapy followed by radiation results in a higher disease-free and distant disease-free survival.

Several cohort studies have examined the effect of sequencing chemotherapy and radiation therapy (47-51). Recht and colleagues reviewed the results of 295 patients with node-positive breast cancer post-lumpectomy receiving radiation therapy and chemotherapy (47). At four years, the crude rate of local recurrence for patients beginning radiation therapy within 16 weeks of surgery was 4% compared with 12% for those beginning radiation therapy ≥ 16 weeks after surgery ($p=0.06$). Buzdar and colleagues (48) reviewed 89 patients with node-negative and -positive breast cancer treated by breast irradiation and adjuvant chemotherapy following lumpectomy. Thirty-nine patients received chemotherapy following radiotherapy and in 46, the therapies were administered in reverse order. The rate of local (3% vs 5%, $p=0.8$) and distant recurrence (28% vs 19%, $p=0.7$) was equivalent between the respective sequences. Other groups have also studied the effect of sequencing of chemotherapy and radiation (49-51). In several large trials evaluating adjuvant chemotherapy in early breast cancer post-lumpectomy, breast irradiation was delayed until chemotherapy was completed without any apparent increase in local breast recurrence (59-61).

An important concern regarding scheduling is the potential for increased acute and late effects of radiotherapy when chemotherapy and radiation therapy are given concurrently, especially when anthracycline-based regimens are used. This observation has been reported in several case series (52-54).

The Avoidance of Breast Irradiation Post-lumpectomy

Original: March 1997

Several approaches to avoid the use of breast irradiation following breast conserving surgery have been studied including: i) attempts to identify a group of patients at low risk for local breast recurrence post-lumpectomy, ii) the use of more extensive local surgery, and iii) the use of systemic adjuvant therapy alone post-lumpectomy.

In the original OCOG study evaluating the role of breast irradiation post-lumpectomy in node-negative patients, the investigators tried to identify a group at low risk for local breast relapse who might be spared breast irradiation (6). Tumour size >2 cm and age <50 predicted

for local relapse. Thus, patients aged 50 years and older who had tumours of 2 cm or less were defined as a possible low risk group. The rate of local relapse for women in this group treated by lumpectomy alone was 13.5% which was felt to be unacceptably high. Similarly, in further follow-up of patients in the NSABP B-06 study, it was noted that although tumour size predicted for local breast recurrence, the risk of recurrence post-lumpectomy for node-negative patients with tumours 1 cm was 25% at 8.5 years (3).

In the Uppsala-Örebro Breast Cancer Study Group trial (4,5), eligibility was limited to node-negative patients with tumours ≤ 2 cm who were treated with a sector resection which was felt to be a more extensive type of surgery than lumpectomy alone. (This surgery can be considered equivalent to quadrantectomy in terms of extent.) In the original report (4), with a follow-up of 2.75 years, the local breast recurrence rate for patients treated with surgery alone was 7.6% indicating that more aggressive surgery might result in an acceptable local recurrence rate. Further follow-up at five years (5), however, has revealed a recurrence rate of 18.4%. Similarly, in the Milan study (8) in which patients were treated with quadrantectomy, the rate of local recurrence with surgery alone with a follow-up of 3.25 years is reported as 8.8%. This lower rate of recurrence needs to be supported by further follow-up, but it appears to be at the expense of a worse cosmetic outcome (55).

With the increasing use of systemic therapy, investigators have evaluated these treatments alone without irradiation post-lumpectomy in preventing local breast recurrence. In an Ontario study for node-positive patients, a subset of 121 premenopausal lumpectomy patients were identified for whom no breast irradiation was given, but for whom a 12- or 36-week course of systemic adjuvant treatment was prescribed. Although local breast recurrences were less frequent with 36 weeks of systemic treatment (CMFVP) than with 12 weeks of treatment (23% vs 39% respectively, $p=0.02$), they were not sufficient to replace the use of breast irradiation (56). Two further randomized trials evaluating breast irradiation plus Tamoxifen versus Tamoxifen alone in post-menopausal women post-lumpectomy are currently ongoing.

Adverse Effects

Original: March 1997

No data on the adverse effects of breast irradiation were included in the original guideline report.

Update: January 2002

This update section summarizes the evidence collected between completion of the guideline in March 1997 and September 1999.

Several additional studies looking at acute and late radiation complications, and carcinogenicity as potential adverse effects of breast irradiation were identified by the update search.

Additional evidence is available from a randomized controlled study (3u) of the ability of aspirin to reduce the late effects of radiation therapy. Skin erythema and fatigue were common short-term side effects of radiation therapy. Mild and moderate long-term side-effects of radiation consisting of breast edema, fibrosis, telangiectasia, and pain or discomfort were noted in 5 to 15 percent of patients treated with breast irradiation following lumpectomy.

Two meta-analyses have suggested that adjuvant radiation after mastectomy may result in increased late cardiac mortality (4u [cited in original practice guideline report],5u). This effect appears most evident for studies of older radiotherapy techniques utilizing orthovoltage (6u,7u) or involved irradiation of the internal mammary nodes (6u-8u) resulting in a large volume of the heart being irradiated. Increased cardiac mortality has not been demonstrated in randomized trials of breast irradiation alone (1u).

The addition of postoperative radiotherapy to sector resection and axillary dissection did not increase arm symptoms (pain, numbness, impaired shoulder mobility, arm swelling) during the

first 36 months after surgery in women who participated in the Uppsala-Orebro Breast Cancer Study (12u).

V. INTERPRETIVE SUMMARY

Original: March 1997

An interpretative summary was not included in the original practice guideline report.

Update: January 2002

The updated evidence, collected between completion of the guideline in March 1997 and September 1999 supports the current guideline. The RCT by Romestaing et al suggests that boost irradiation may further decrease the risk of local recurrence in patients with clear resection margins. However, the event rate is low and further follow-up is necessary to confirm these findings.

VI. ONGOING TRIALS

The following randomized trials were listed in the PDQ Clinical Trials database in January 2002:

- CAN-NCIC-MA20: Phase III randomized study of adjuvant breast radiotherapy with or without regional radiotherapy in women with resected, early stage, invasive breast cancer.
- EORTC-10925, EORTC-22922: Phase III randomized study of internal mammary and medial supraclavicular lymph node chain irradiation vs no further therapy in women with resected stage I/II/III breast cancer.
- STMG-STARTB, EU-99015: Phase III randomized study of radiotherapy fractionation regimens after local excision or mastectomy in women with early stage breast cancer
- CRC-TU-BR3015, EU-99005: Phase III randomized study of synchronous versus sequential adjuvant chemotherapy and radiotherapy in women with early stage breast cancer.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Original: March 1997

There have been four randomized trials of breast irradiation following breast conserving surgery in women with early stage disease (3,5,6,8). These studies have consistently demonstrated a reduction in the risk of local breast recurrence ranging from 73 to 89%. In these studies, there has been no survival impact from the use of breast irradiation. The impact of breast irradiation on quality of life has not been well studied, but reported major adverse effects of breast irradiation have occurred very infrequently, and the majority of patients report a good or excellent cosmetic outcome. In discussion, the group felt that despite the failure to demonstrate a difference in survival between radiated and non-radiated patients, breast irradiation should be offered to women post-lumpectomy to reduce the risk of local breast recurrence. This was felt to be an important outcome resulting in an increase in breast conservation and avoidance of potential psychological upset associated with a recurrence.

The optimal fractionation schedule for breast irradiation has not been established. Indirect comparisons between studies suggest that several commonly used schedules are comparable. Several randomized clinical trials comparing currently used fractionation schedules are in progress. Patient participation in these studies should be encouraged. In discussion, the group felt that outside a clinical trial, patients should be treated with radiation schedules that have proven to be effective in reducing local recurrence with minimal toxicity. Consideration was given to several schedules. Two schedules with established efficacy following lumpectomy which have been used widely in Ontario were suggested: 5000 cGy in 25 fractions to the whole breast or 4000 cGy in 16 fractions to the whole breast with a local boost to the primary site of 1250 cGy in five fractions. Shorter schedules, e.g., 4400 cGy in 16 fractions or 4000 cGy in 16 fractions have also been used routinely in some centres and there are no randomized trials that demonstrate inferior efficacy of such schedules (57,58). Further evidence regarding the use of shorter radiation schedules should be forthcoming from ongoing clinical trials.

No randomized trials directly comparing different intervals of commencing radiation post surgery were identified. Of the randomized trials considered in our review, the maximum interval between surgery and the commencement of radiation was 12 weeks in the OCOG node-negative trial (6). In discussion, the group felt that the greatest weight should be put on the results of this study because it was based on patients recruited from our own Ontario centres.

With respect to sequencing of breast irradiation and adjuvant chemotherapy in patients eligible for this treatment, only one published randomized trial was identified. The group felt little weight could be placed on case series because of the concern of selection bias, confounders and small numbers. It was recommended that until further data become available, adjuvant chemotherapy (when appropriate) should be instituted as soon as possible following surgery. Breast irradiation should be initiated following completion of chemotherapy. Concurrent chemotherapy and radiation should be avoided when using anthracycline-containing regimens in view of the potential for increased acute and late toxicity.

A group of patients at low risk for local breast recurrence who might be spared breast irradiation cannot be identified at present but clinical trials evaluating the role of Tamoxifen are ongoing.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Original: March 1997

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Practice Guideline

Based on the evidence contained under the Original subtitles throughout this report, the Breast Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with early stage (stages I and II) invasive breast cancer whom have had breast conserving surgery.

Draft Recommendations

- Women with early stage (stages I and II) breast cancer who have undergone breast conserving surgery should be offered postoperative breast irradiation.
- The optimal fractionation schedule for breast irradiation has not been established. It is recommended that patients participate in ongoing clinical trials evaluating different fractionation schedules. Outside of a clinical trial, the role of boost irradiation is unclear. Two commonly used fractionation schedules are suggested: 5000 cGy in 25 fractions to the whole breast, or 4000 cGy in 16 fractions to the whole breast with a local boost to the primary site of 1250 cGy in five fractions. Shorter schedules, e.g., 4400 cGy in 16 fractions or 4000 cGy in 16 fractions have also been used routinely in some centres. There are no randomized trials that demonstrate inferior efficacy of such schedules.
- Women who have undergone breast conserving surgery should commence local breast irradiation as soon as possible following wound healing. A safe window between surgery and commencement of radiation is unknown, but it is reasonable to commence breast irradiation within 12 weeks of definitive surgery.
- For patients who are candidates for chemotherapy the optimal sequencing of chemotherapy and radiation is not known. It is reasonable to institute radiation following completion of chemotherapy or concurrently when anthracycline-containing regimens are not used.

Practitioner Feedback

Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 100 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Breast Cancer Disease Site Group.

Results

Sixty-nine (69%) surveys were returned. Sixty-six (95%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Ninety-five percent agreed or strongly agreed with the methods and data synthesis, 95% endorsed the evidence-based report, and 88% endorsed the evidence-based report as a practice guideline.

Of the respondents who provided written comments, the main points were concern over the role of axillary lymph node dissection in the following circumstances: when positive margins are present, age of patient, number of nodes involved.

Of the respondents who provided written comments, the main points were:

1. The recommendation should encourage participation in a broader range of clinical trials.
2. A description/definition of clear resection margins would be helpful.

Modifications/Actions

1. As a result of practitioner feedback, there is one minor difference between the evidence-based recommendation and the practice guideline. The guideline recommends that patients participate in 'ongoing clinical trials' rather than in 'trials evaluating different fractionation schedules' as suggested in the EBR.
2. The DSG has added the definition of 'clear resection margins' used by several cooperative groups (2,6) to page 1 of the guideline report.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Breast Cancer DSG and the Practice Guideline Coordinating Committee.

- Women with early stage (stages I and II) breast cancer who have undergone breast conservation surgery (defined as excision of the tumour with clear resection margins) should be offered postoperative breast irradiation.
- The optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. Outside of a clinical trial, two commonly used fractionation schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions. Shorter schedules (e.g., 40 or 44 Gy in 16 fractions) have also been used routinely in some centres. The enrolment of patients in ongoing clinical trials is encouraged.
- Women who have undergone breast conserving surgery should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery.

- For women who are candidates for chemotherapy, the optimal sequencing of chemotherapy and radiotherapy is unknown. It is reasonable to start radiotherapy after the completion of chemotherapy, or concurrently if anthracycline-containing regimens are not used.

IX. PRACTICE GUIDELINE

This practice guideline reflects the evidence from the original guideline report plus the new evidence up to September 1999. The Breast Cancer DSG is in the process of rewriting the guideline report. The current guideline recommendations remain in effect.

Target Population

These recommendations apply to adult patients with early stage (stages I and II) invasive breast cancer whom have had breast conserving surgery.

Recommendations

- Women with early stage (stages I and II) breast cancer who have undergone breast conservation surgery (defined as excision of the tumour with clear resection margins) should be offered postoperative breast irradiation.
- The optimal fractionation schedule for breast irradiation has not been established and the role of boost irradiation is unclear. Outside of a clinical trial, two commonly used fractionation schedules are suggested: 50 Gy in 25 fractions to the whole breast, or 40 Gy in 16 fractions to the whole breast with a local boost to the primary site of 12.5 Gy in five fractions. Shorter schedules (e.g., 40 or 44 Gy in 16 fractions) have also been used routinely in some centres. The enrolment of patients in ongoing clinical trials is encouraged.
- Women who have undergone breast conserving surgery should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery.
- For women who are candidates for chemotherapy, the optimal sequencing of chemotherapy and radiotherapy is unknown. It is reasonable to start radiotherapy after the completion of chemotherapy, or concurrently if anthracycline-containing regimens are not used.

X. JOURNAL REFERENCE

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XI. ACKNOWLEDGEMENTS

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For a full list of members of the Cancer Care Ontario Breast Cancer Disease Site Group please visit the website of the Program in Evidence-based Care at <http://www.cancercare.on.ca/ccopgi>.

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Appendix 1. Joint American UICC* staging classification for breast cancer.

Stage I: Tumour is 2 cm or less in its maximum diameter and is localized to the breast with no involvement of regional nodes.

Stage II: Tumour is more than 2 cm, but not larger than 5 cm in its greatest dimension, or has metastasized to the axillary nodes which are not fixed.

Stage III: Tumour is larger than 5 cm or has locally invaded beyond the breast parenchyma, as manifested by infiltration of the skin or extension to underlying muscles and fascia or axillary nodes are fixed to one another.

Stage IV: Distant metastases.

* UICC International Union Against Cancer: *TNM Classification of Malignant Tumours, 4th Ed.* Hermanek P & Sobin LH (Eds). Berlin: Springer-Verlag, 1987.

Table 1. Randomized trials comparing lumpectomy plus radiation therapy with lumpectomy alone.

Trial	Patient No.		Intervention	Interval Between Surgery and RT	Outcome Measures	Local Recurrence RT vs No RT	Survival RT vs No RT
	RT	NO RT					
Fisher (2)	567	570	Mastectomy, lumpectomy or lumpectomy + RT (50 Gy/25)	# 8 weeks	Local recurrence; 12 y survival	Node -ve 12% vs 32% Node +ve 5% vs 41% p for both <0.001	62% vs 60% NS
Clark (6)	416	421	Lumpectomy or lumpectomy + RT (40 Gy/16 + a boost of 12.5 Gy/5)	#12 weeks	Disease relapse; 4 y survival	Node -ve 5.5% vs 25.7% p<0.0001	92% vs 91% NS
Uppsala-Örebro (5)	184	197	Lumpectomy or lumpectomy + RT (54 Gy/27)	# 12 weeks	Local recurrence; 5 y survival	Node -ve 2.3% vs 18.4% p<0.0001	91% vs 90.3% NS
Veronesi (8)	299	280	Quadrantectomy or quadrantectomy + RT (50 Gy/25 + a boost of 10 Gy/5)	4 to 6 weeks	Local recurrence; 4 y survival	Node -ve 0.3% vs 8.8% p<0.001	No difference (data not available)

Table 2. Randomized trials comparing lumpectomy plus radiation therapy with mastectomy.

Trial	Patient No.		Intervention	Interval Between Surgery and RT	Outcome Measures	Local Recurrence Lump + RT	Survival Lump + RT vs Mastectomy
	Lump	Mast					
Fisher (2)	714	682	Mastectomy, lumpectomy or lumpectomy + RT (50 Gy/25)	# 8 weeks	Local recurrence; 12 y survival	10%	62% vs 62% NS
Van Dongen (30)	456	526	Mastectomy or breast conserving surgery + RT (50 Gy/25 + boost of 25 Gy)	# 6 weeks	Local recurrence; 8 y survival	9.3%	77% vs 79% NS
Blichert-Toft (31)	450	455	Mastectomy or breast conserving surgery + RT (50 Gy/25 + boost of 10-25 Gy/5-12)	2 to 4 weeks*	Disease recurrence; 6 y survival	2.4%	79% vs 82% NS
Veronesi (32)	352	349	Mastectomy or quadrantectomy + RT (50 Gy/25 + boost of 10 Gy/5)	# 3 weeks	Local recurrence; 7 y survival	0.3%	83% vs 83.5% NS
Straus (33)+	121	116	Mastectomy or lumpectomy + RT (48.6 Gy/27 + boost of 15-20 Gy)	Not available	Local recurrence; 5 y survival	13%	89% vs 85% NS
Sarrazin (34)	88	91	Mastectomy or lumpectomy + RT (45 Gy/18 + boost of 15 Gy/6)	Not available	Local recurrence; 10 y survival	7%	79% vs 80% NS

*Time from surgery to referral for RT