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

*Members of the Breast Cancer Disease Site Group*

This Evidence-Based Series (EBS) was reviewed and designated as Education & Information by the Breast Cancer Disease Site Group (DSG).

(See Section 4: Document Summary and Review Tool for details.)

The reviewed EBS report, which is available on the CCO web site (http://www.cancercare.on.ca), consists of the following four sections:

- **Section 1:** Clinical Practice Guideline (Education & Information)
- **Section 2:** Full Report
- **Section 3:** Guideline Review Summary and Tool, 2011
- **Section 4:** Guideline Review Summary and Tool, 2016

October 11, 2016

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Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca

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

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<tr>
<td>Original version</td>
<td>1966 to 1996</td>
<td>Peer review</td>
<td>Search updated in Apr 1997 and Sept 1999 but no changes made to recommendations</td>
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<tr>
<td>Feb 1997</td>
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<td>Update Mar 2002</td>
<td>1996 to 2001</td>
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<td>Education and Information</td>
<td>2010 to 2016</td>
<td>New data in 2016 Guideline Review</td>
<td>Web publication 2002 with 2011 assessment as Section 3 and 2016 assessments as Section 4.</td>
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</tbody>
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Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast Conserving Surgery

Practice Guideline Report #1-2


Please see the Review Summary for updated evidence published between 2010 and 2016.

Report Date: January 2002

SUMMARY (Section 1)

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 CANCERLIT 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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The Practice Guidelines Initiative is sponsored by:
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Visit http://www.cancercare.on.ca for all additional Practice Guidelines Initiative reports.
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:

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Breast Irradiation in Women with Early Stage Invasive Breast Cancer 
Following Breast Conserving Surgery 
Practice Guideline Report #1-2

Please see the EBS 1-2 Version 2 Guideline Review Summary 
and the Document Assessment & Review Tool 
Please see the Review Summary for updated evidence published 
between 2010 and 2016.

Report Date: January 2002
FULL REPORT (Section 2)

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, 
mastectomy. 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

2 For further information about the efficacy of lumpectomy in the treatment of early stage breast cancer, please 
refer to the PEBC Practice Guideline 1-1 Version 3: Surgical Management of Early Stage Breast Cancer (Stage I and 
II).
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 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

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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.

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

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

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

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

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 OCG 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 OCG 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

XI. ACKNOWLEDGEMENTS
The Breast Cancer Disease Site Group would like to thank Drs. T. Whelan, B. Lada, E. Laukkanen, F. Perera and M. Levine for taking the lead in drafting and revising this practice guideline report.

The Breast Cancer Disease Site Group would like to thank Wendy Shelley for taking the lead in updating this practice guideline report.

For a full list of members of the PEBC Breast Cancer Disease Site Group please visit the Cancer Care Ontario Web site at http://www.cancercare.on.ca/.
REFERENCES

Original: March 1997


58. Shelley W. Personal communication. 1995.


**Update: January 2002**


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.

Evidence-based Series 1-2 Version 2. Section 3

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

Guideline Review Summary

Review Date: November 19, 2010

The 2002 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 1997; the first update released in March 2002. In November 2010, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Summary and the Full Report in this version are the same as in the March 2002 version.

Update Strategy

Using the Document Assessment & Review Tool as the updating strategy, the PEBC review includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

• 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?

Literature Search and New Evidence

The new search (January 2002 through July 2010) yielded five relevant new
publications of two clinical guidelines, one new randomized controlled trial (RCT) and two RCTs whose initial publications were already included in the original document. Brief results of these publications are shown in the Document Assessment & Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the Breast Cancer DSG ENDORSED the 2002 recommendations on breast irradiation in women with early stage invasive breast cancer following breast conserving surgery.

The opinion was that the current recommendations did not address issue of boost and/or partial radiotherapy, but, at the time of this review, the available data on this issue is not very strong. Pending the availability of new data on boost and/or partial radiotherapy, the guideline and its recommendations are ENDORSED.
<table>
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<td>Clinical reviewer</td>
<td>Dr. Ian S. Dayes</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>R. Bryan Rumble</td>
</tr>
<tr>
<td>Date initiated</td>
<td>July 16, 2010</td>
</tr>
<tr>
<td>Date and final results / outcomes</td>
<td>November 19, 2010 (ENDORSED)</td>
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**Instructions.** Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document as is? Answer Yes or No, and explain if necessary:

   - **1. YES**
     - If No, then the document should be **ARCHIVED** with no further action; go to 11. If Yes, then go to 2.

2. Are all the current recommendations based on the current questions *definitive* or *sufficient*, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:

   - **2. NO**, last search date >5 years ago in December 2001
     - If Yes, the document can be **ENDORSED** with no further action; go to 11. If No, go to 3.

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:

   - **3. NO**
     - If Yes, the document should be taken off the website as soon as possible. A **WARNING** should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.

4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:

   - **4. YES**
     - there is a designated research co-ordinator at the PEBC to carry out the literature search
     - If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.
5a. Guideline Research Questions. Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The DART process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this DART form and answer NO).

- No changes to the guideline questions.

Original Question(s):
- 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.

5b. Inclusion and Exclusion criteria. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).

- No changes to the inclusion or exclusion criteria.

Inclusion Criteria:
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.

Exclusion Criteria:
None specified.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.
Full Selection Criteria, including Types of Evidence (e.g., randomized, non-randomized, etc.):

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.

Exclusion Criteria:
None specified.

Search Period:
- 1996 to July (week 1) 2010 (Medline) (exclude 2001 and earlier)
- Cochrane Database of Systematic Reviews
- Guidelines.gov
- 2005 to 2009 (ASTRO Annual Meetings)
- 2006, 2008 (ESTRO Biennial Meetings)
- 2009 (CARO Annual Meeting)

Brief Summary/Discussion of New Evidence:
Medline: 151 hits, 17 ordered for full-text review, 2 retained.
Cochrane: 3 ordered for full-text review, 0 retained.
Guidelines.gov: One ordered for full-text review, 0 retained.
ASTRO: One ordered for full text review, 0 retained.
ESTRO: None ordered for full text review.
CARO: None ordered for full text review.

Search of references list from the 2 MEDLINE articles found 3 more papers of RCTs.

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<th>Outcomes</th>
<th>Brief results</th>
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<td>Airc study</td>
<td>579 women with carcinoma of the breast</td>
<td>IBTR, OS</td>
<td>RT for all patients under 55 years of age, with 've nodes, or with extensive intraductal component on histology. RT not indicated for women aged over 65 years or for women aged 56-65 years with 've nodes.</td>
<td>Veronesi et al, 2001; (update of reference 8 in current document)</td>
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<td>BCS+TAM vs. BCS+RT vs. BCS+TAM+RT</td>
<td>NSABP B-21</td>
<td>1009 women with invasive breast cancer</td>
<td>IBTR, contralateral breast cancer, OS</td>
<td>RT should be given post-lumpectomy regardless of tumour ER status, and TAM should be given if ER+ve</td>
<td>Fisher et al, 2002</td>
</tr>
<tr>
<td>BCS+TAM vs.</td>
<td>Calgb-C9343</td>
<td>636 women aged 70 years or older</td>
<td>Local recurrence,</td>
<td>No benefit to addition of RT to BCS+TAM for</td>
<td>Hughes et al, 2004; (update</td>
</tr>
</tbody>
</table>
BCS+TAM+RT with ER+ve breast cancer treated by lumpectomy regional recurrence, distant metastases, OS (5-year) women aged 70 years or older of reference 23u in current document

+ve = positive; BCS = breast conserving surgery; ER = estrogen receptor; IBTR = intra-breast tumour reappearance; RCT = randomized controlled trials; OS = overall survival; RT = radiotherapy; TAM = tamoxifen; vs. = versus.

2 related clinical practice guidelines were also found.

<table>
<thead>
<tr>
<th>Topic of guideline</th>
<th>Year of guideline</th>
<th>Brief summary</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast RT after BCS</td>
<td>2003</td>
<td>Following BCS, whole breast RT remains standard treatment</td>
<td>Whelan et al, 2003</td>
</tr>
<tr>
<td>RT of breast cancer</td>
<td>2007</td>
<td>Following BCS, whole breast RT remains standard treatment</td>
<td>Sautter-Bihl et al, 2007</td>
</tr>
</tbody>
</table>

BCS = breast conserving surgery; RT = radiotherapy

New References Identified (alphabetical order):


**Literature Search Strategy:**

**Medline**
Database: Ovid MEDLINE(R) <1996 to July Week 1 2010>
Search Strategy:

1. Breast neoplasms/rt [Radiotherapy] (5365)
2. breast.tw. (131555)
3. mammary.tw. (22411)
4. 2 or 3 (145740)
5. cancer.tw. (474187)
6. carcinoma.tw. (176582)
7. neoplasm.tw. (16931)
8. 5 or 6 or 7 (589722)
9. radiotherapy/ or radiotherapy, adjuvant/ (23504)
10. radiotherapy.tw. (51462)
11. radiation.tw. (97325)
12. irradiat..tw. (64203)
13. 9 or 10 or 11 or 12 (177401)
14. 4 and 8 and 13 (9805)
15. 1 or 14 (11528)
16. RANDOMIZED CONTROLLED TRIALS/ (58828)
17. randomized controlled trials.pt. (0)
18. 16 or 17 (58828)
19. 15 and 18 (439)
| 20 | limit 19 to yr=2002-2010 (301) |
| 21 | review.pt. (999544) |
| 22 | 20 not 21 (151) |
| 23 | from 22 keep 1-151 (151) |

**Cochrane**  
Keywords: Breast, radiation

**Guidelines.gov**  
Keywords: Breast, radiation

**ASTRO**  
Keywords: Breast (Title, abstract)

**ESTRO**  
Keywords: Breast (Title, abstract)

**CARO**  
Keywords: Breast (Title, abstract)

---

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?

<table>
<thead>
<tr>
<th>6. NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, then the document should be <strong>ARCHIVED</strong> with no further action; go to 11. If No, go to 7.</td>
</tr>
</tbody>
</table>

7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:

<table>
<thead>
<tr>
<th>7. YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>The additional evidence continues to support the recommendations.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>The recommendations do not cover all relevant subjects because it does not address the current issues of boost and/or partial radiotherapy.</td>
</tr>
<tr>
<td>The data for boost and partial radiotherapy are not very strong at present and more publications are expected to arise in the future (in about 5 years time).</td>
</tr>
<tr>
<td>When the new data becomes available, it may result in either an update of guideline 1-2 or archiving of guideline 1-2 followed by the production of a brand new guideline with new research Qs.</td>
</tr>
<tr>
<td>Therefore at this time, Guideline 1-2 can be <strong>ENDORSED</strong>.</td>
</tr>
</tbody>
</table>

If Yes, the document can be **ENDORSED**. If No, go to 8.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

<table>
<thead>
<tr>
<th>Answer</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>8. Not applicable.</td>
</tr>
</tbody>
</table>

If Yes, a **WARNING** note will be placed on the web site. If No, go to 9.

9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

<table>
<thead>
<tr>
<th>Answer</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>9. Not applicable.</td>
</tr>
</tbody>
</table>

If Yes, the document update will be **DEFERRED**, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.

10. An update should be initiated as soon as possible. List the expected date of completion of the update:

<table>
<thead>
<tr>
<th>Answer</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>10. Not applicable.</td>
</tr>
</tbody>
</table>

An **UPDATE** will be posted on the website, indicating an update is in progress.

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

| DSG Approval Date | November 19, 2010 |
STEP 1: Initiation of the Document Assessment & Review process

STEP 2: First teleconference to determine:
- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

#1. Is there still a NEED for a guideline covering one or more of the topics in this document?

Yes → Archive

No → RC emails DSG reviewer(s) the protocol

#2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?

Yes → Endorse

No →

#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?

Yes → Warning

No →

#4. Do current resources allow for an updated literature search to be conducted at this time?

Yes → New search

No → Deferral

#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

STEP 3: A NEW literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date.

Discuss questions #1-5

Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.

Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria.
**FLOW CHART (cont.)**

### STEPS

**Action**

**STEP 4:** Second teleconference to determine the ultimate status of the document

<table>
<thead>
<tr>
<th>#6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?</th>
<th>Yes</th>
<th>Archive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#7. Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?</th>
<th>Yes to all</th>
<th>Endorse</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?</th>
<th>Yes</th>
<th>Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#9. Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?</th>
<th>Yes</th>
<th>Deferral</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#10. An update should be initiated as soon as possible. List the expected date of completion of the update.</th>
<th>Yes</th>
<th>Update⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STEP 5:** Final outcome approval; Document Assessment & Review questions #11

<table>
<thead>
<tr>
<th>#11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.</th>
<th></th>
<th></th>
</tr>
</thead>
</table>
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.
The 2002 guideline recommendations (as endorsed 2011) are designated as

EDUCATION & INFORMATION

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

BACKGROUND

Original Version: March 11, 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. The literature search using MEDLINE and CANCERLIT was conducted 1966- January 1996.

Comment: Regular literature searches subsequent to document completion and prior to the January 2002 update were made; new studies appear to have been added April 1997 and September 1999 with notes that there was no change to recommendations.

Update: January 2002

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.
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.

Comment: The new trials are listed and data extracted, however the document indicates in several places that “the Breast Cancer DSG is in the process of rewriting the guideline report. The current guideline recommendations remain in effect.” It is unclear whether a rewrite ever occurred, but appears not to have, as these statements still appear in the subsequent version (Version 2: January 2002 version plus document assessment appended).

Assessment 2010 (started July 16, 2010, completed November 19, 2010)

The literature search included MEDLINE (1996 to July (week 1) 2010, excluding 2001 and earlier), Cochrane Database of Systematic Reviews, Guidelines.gov, 2005 to 2009 ASTRO Annual Meetings (2005-2009), ESTRO Biannual Meetings (2006, 2008), CARO Annual Meeting (2009). The MEDLINE search only included articles indexed as “randomized controlled trials/” and excluded “review.pt”. Only 154 hits were found and 2 retained, plus another 3 from reference lists.

Comment: This appeared to be a very narrow/focused review designed to give some idea as to whether an update might be required, but not to the level of a systematic review. If an update of this guideline is eventually deemed necessary, it is recommended that the literature search from the 2010 assessment not be used. A new broader search including both MEDLINE and EMBASE would be needed, or reliance on a review by another organization.

Conclusion of 2010 review: Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the Breast Cancer DSG ENDORSED the 2002 recommendations on breast irradiation in women with early stage invasive breast cancer following breast conserving surgery.

The opinion was that the current recommendations did not address issue of boost and/or partial radiotherapy, but, at the time of this review, the available data on this issue is not very strong. Pending the availability of new data on boost and/or partial radiotherapy, the guideline and its recommendations are ENDORSED.

2016 ASSESSMENT

In 2016 this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (GGF) conducted an updated search of the literature. GGF and a clinical expert (ISD) reviewed and interpreted the new eligible evidence and proposed that the exiting evidence-based series be designated as “Education & Information”. The Breast Cancer Disease Site Group (DSG) members agreed with this assessment, and the document was designated as Education & Information on October 11, 2016. The assessment tool and summary of new evidence is provided in the following pages.
Number and Title of Document under Review | 1-2 Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast Conserving Surgery
---|---
Current Report Date | September 15, 2011, Version 2. This was an endorsement of the March 2002 update of the original version dated February 1997
Clinical Expert | Ian S. Dayes
Health Research Methodologist | Glenn G. Fletcher
Date Assessed | September 13, 2016
Approval Date and Review Outcome | Education & Information October 11, 2016

Original Question(s):
- 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.

Study Section Criteria:
Randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines

Search Details:
Medline and Embase (1996- April 2016), EBM Reviews - Cochrane Database of Systematic Reviews (2005 to April 07, 2016) and Cochrane Central Register of Controlled Trials February 2016 were searched. RCTs were screened and data extracted only for the period 2009-2016, while reviews were looked at from 2010-2016. The search strategy was designed to capture all articles dealing with both breast cancer and radiotherapy. Of 13247 records (plus 22 from
additional sources), 72 RCTs (156 publications), 32 guidelines, and 31 systematic reviews or meta-analyses were identified.

**Summary of New Evidence:** See section following this table

**Clinical Expert Interest Declaration:** No conflicts declared

<table>
<thead>
<tr>
<th>1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)</th>
<th>No. The recommendation to give RT to patients with BCS is still supported. In addition to recurrence benefit found in the initial guideline, there is now survival benefit, as shown in the EBCTCG meta-analysis. The original guideline indicated that the optimal fractionation schedule has not been established and the role of boost irradiation is unclear. Data now suggests hypofractionation (39-42 Gy in 13-16 fractions) is preferred over 50 Gy in 25 fractions. Data on boost irradiation is available and has been incorporated into clinical practice.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Does the newly identified evidence support the existing recommendations?</td>
<td>Yes, but evidence now available would support much more detailed and informative recommendations.</td>
</tr>
<tr>
<td>3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)</td>
<td>No. See above for hypofractionation and boost. The guideline does not address partial breast irradiation; several major trials are ongoing and data may be insufficient at this time for a clear recommendation. The guideline does not address irradiation of the axilla. Results from several RCTs are now available. This topic will be included in PEB/C/CCO guideline 1-23: “Management of the Axilla in Early-Stage Breast Cancer” (expected completion late 2017).</td>
</tr>
<tr>
<td>4. Is there a good reason to postpone updating the guideline? (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations)</td>
<td>Yes, see 3 above. ASTRO is updating their guideline on WBI (expected completion May 2017), and it will cover most of the questions except PBI. It is suggested that this guideline be looked at for possible endorsement when completed. NICE is also updating their guideline on early and locally advanced breast cancer (expected completion 2018).</td>
</tr>
<tr>
<td>Review Outcome as recommended by the Clinical Expert</td>
<td>Move to “Education and Information”.</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>While very outdated, an update is unlikely to change current practice as hypofractionated WBI with boost after BCS is already widely used in Ontario.</td>
<td></td>
</tr>
</tbody>
</table>

**SUMMARY OF NEW EVIDENCE, 2016**

The accompanying tables provide information on guidelines, systematic reviews and meta-analyses, and randomized controlled trials located in the literature review. A summary for some of the major questions is given below.

**RT after BCS**

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) published an individual patient meta-analysis [1] focused on RT after BCS. It included 10,801 women from 17 RCTs (compared to 4 trials in the original PEBC guideline) and reported 10-year recurrence and 15-year breast cancer death rates. It found RT halved the rate of recurrence and reduced breast cancer death rate by about a sixth. Proportional benefit varies little between different groups but absolute benefit varies substantially depending on patient/disease characteristics. Some of the 12 trials on RT after BCS identified in the current search are likely included in or updates of those in the EBCTCG meta-analysis.

There is an ACR guideline on this topic [2] with literature included from Medline until August 2014. Some trials may be missing as it did not include a search of other databases, but it is expected to be much more complete than the current PEBC guideline. ASTRO is in the process of preparing a guideline on whole breast irradiation (expected completion May 2017) covering topics of dose/fractionation schemes, boost, and treatment planning.

**RT after BCS in Elderly Patients**

CALGB 9343 trial [3] is the basis of the NCCN recommendation not to use RT in elderly HR+ patients receiving tamoxifen.

The meta-analysis by Van de Water [4] found a small decrease in LRR but no effect on OS in 5 trials (3190 pts) [including the CALGB trial] and concluded both treatment options may be reasonable.

**Fractionation**

Current key evidence indicates that four randomized trials and two retrospective studies were identified and that the optimal fractionation schedule cannot be established. Note that 3 of the 4 trials were ongoing. In the current search, the START pilot, START A, START B, Canadian Hypofractionation Trial (OCOG-1993-hypo), West Midlands Oncology Breast Cancer Group, and Cairo trials reported survival and/or recurrence data; several others reported toxicity/cosmesis data or are ongoing.

ASTRO is in the process of preparing a guideline on whole breast irradiation (expected completion May 2017), covering topics of dose/fractionation schemes, boost, and treatment planning.
planning. Cancer Australia has a guideline with literature up to November 2013 on the topic of hypofractionated radiotherapy [5].

Timing

None of the 3 trials included in the Cochrane review (meta-analysis) by Hickey et al [6] were included in the current PEBC version; key publications were in the period 2004-2006 and should have been found in the updated search during the previous assessment. The current search found the CO-HO-RT trial (concurrent or sequential letrozole) which was published in 2010 [7], with final result in 2016 [8]. There are several abstracts of the SECRAB trial which included 2296 patients.

Boost

The EORTC-22881-10882 trial reported lower recurrence but greater incidence of fibrosis and worse cosmetic outcome with boost. In other trials, results for cosmesis tended to be better with lower boost doses. It is expected that this will be covered in the ASTRO guideline on whole breast irradiation (expected completion May 2017).

IMRT

The IMPORT LOW trial suggests PBI is non-inferior, though 10-y results are not yet available. In the Cambridge IMRT trial there fewer patents developed suboptimal cosmesis and skin telangiectasia. Other trials are ongoing. A guideline by the Sociedade Brasileira de Radioterapia covered literature until July 2013 [9].

IORT

The TARGIT A found superior results with TARGIT compared to WBI. The ELIOT trial found worse recurrence but few skin side effects with ELIOT.

Partial Breast Irradiation

The GEC-ESTRO trial found APBI well tolerated and not inferior. The Florence trial found APBI better, while the Budapest trial found PBI similar to WBI and with better cosmetic results. Several other large trials (NSABP B-39, RAPID, SHARE, IRMA, DBCG PBI) are ongoing. The Blue Cross/Blue Shield guideline covers data until November 2014, while the American Brachytherapy Society, GEC-ESTRO, and ASTRO cover literature to 2012, 209, and 2008, respectively.

Nodal Irradiation

Trials either compared axillary RT to ALND or to no axillary treatment. AMOROS (EORTC 10981-22023) found comparable axillary control but less lymphedema with RT compared to ALND. OTOASOR also found RT did not increase risk of axillary failure. Trials by Bing et al found similar breast cancer survival and metastasis-free survival with RT compared to axillary clearance but more axillary recurrence.

EORTC 22922 and MA.20 compared nodal irradiation to no nodal treatment and found improvement in recurrence /DFS but not OS with RT. The GRISO trial found improvement of
distant metastases. Several other large trials are ongoing (NSABP B-51/RTOG 1304, KROG 08-06, UK-ANZ POSNOC).

The PEBC is starting work (June 2016) on a guideline on Management of the Axilla in Early-Stage Breast Cancer (PEBC 1-23).
### Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Author; Citation</th>
<th>Title</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RT after BCS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEGRO: German Society of Radiation Oncology, Sedlmayer, 2013 [10]</td>
<td></td>
<td>Radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer</td>
<td>Lists search terms but not further details; update of 2007 version; references until 2013</td>
</tr>
<tr>
<td><strong>Portion on RT after BCS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Whole breast irradiation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypofractionation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Organization</td>
<td>Author; Citation</td>
<td>Title</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
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<tr>
<td><strong>Partial breast irradiation</strong></td>
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</tr>
<tr>
<td><strong>IMRT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Care Ontario</td>
<td>Dayes, 2012 [22]</td>
<td>Intensity-modulated Radiotherapy in the Treatment of Breast Cancer</td>
<td>Medline, Embase until March 2009; websites, ASTRO abstracts -insufficient data to recommend over tangential radiotherapy after BCS for reasons of oncological outcomes or late toxicity; need more long-term studies-recommended for avoidance of acute adverse effects</td>
</tr>
<tr>
<td><strong>Other issues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEBC</td>
<td>PEBC (in progress) [23]</td>
<td>Management of the Axilla in Early-Stage Breast Cancer. PEBC 1-23</td>
<td>In early planning stage; estimated completion late 2017 or early 2018</td>
</tr>
<tr>
<td>DEGRO: German Society of Radiation Oncology, Sautter-Bihl, 2014 [24]</td>
<td>Radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways</td>
<td>Comprehensive literature search (no details; references until 2013)</td>
<td></td>
</tr>
<tr>
<td>ACR: American College of Radiology</td>
<td>Halyard, 2013 [25]</td>
<td>ACR Appropriateness Criteria local-regional recurrence (LRR) and salvage surgery-breast cancer</td>
<td>Comprehensive search in Medline (last references from 2012); methodology for series given in separate document</td>
</tr>
<tr>
<td>Organization</td>
<td>Author; Citation</td>
<td>Title</td>
<td>Comments</td>
</tr>
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<td>--------------</td>
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<td>----------</td>
</tr>
<tr>
<td>edition</td>
<td>systematic review</td>
<td>-EORTC 22881-10882 [27] as evidence for boost and 50 Gy in 25 fractions -Canadian, START-A and START-B for hypofractionated WBI -APBI: see ASTRO/ESTRO task force for pt criteria; need longer follow-up of TARGIT</td>
<td></td>
</tr>
<tr>
<td>General Breast Cancer Guidelines</td>
<td></td>
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<tr>
<td>AGO: German Gynecological Oncology Group Hanf, 2015 [31]</td>
<td>AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2015</td>
<td>“evidence-based recommendations”; no details of search; section on Adjuvant radiotherapy (1 page); refers to AGO and DEGRO consensus and differences</td>
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<tr>
<td>SIGN: Scottish Intercollegiate Guidelines Network</td>
<td>SIGN 134. Treatment of primary breast cancer. A national clinical guideline</td>
<td>Medline, Embase, CINAHL, PsychINFO, Cochrane 2003-2011 Section 4.1 is on RT after BCS (1 page) and 4.2 on boost RT</td>
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<tr>
<td>Guideline Program in Oncology of the AWMF (Association of the Scientific Medical Societies of Germany), the German Cancer Society (Deutsche Krebsgesellschaft e.V.) and German Cancer Aid Kreienberg, 2013 [33]</td>
<td>Interdisciplinary GoR level III guidelines for the diagnosis, therapy and follow-up care of breast cancer</td>
<td>Short version; full version is in German (S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer) Gives evidence for recommendation but no details of literature (may be in full document) 4.6.1 on RT after BCS 4.6.2 on partial breast irradiation</td>
<td></td>
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<tr>
<td>Organization</td>
<td>Author; Citation</td>
<td>Title</td>
<td>Comments</td>
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<tr>
<td>BMJ Clinical Evidence</td>
<td>Stebbing, 2011</td>
<td>Breast cancer (non metastatic). Systematic review</td>
<td>Medline, Embase, Cochrane to April 2009 - RT after BCS has reduced local recurrence and breast cancer mortality - PBI, RT to internal mammary chain or ipsilateral supraclavicular fossa after BCS have unknown effectiveness (pp 34-36)</td>
</tr>
<tr>
<td>NICE</td>
<td>2009 [35-37]</td>
<td>Breast cancer (early and locally advanced): diagnosis and treatment</td>
<td>Various databases (Medline, Embase, Cochrane, CINAHL and others): dates vary depending on question but include until about April 2008 Chapter 6 on adjuvant radiotherapy 2015 assessment [38] concludes guideline needs update. AMAROS trial is of relevance to RT of the axilla</td>
</tr>
</tbody>
</table>
### Meta-Analyses and Systematic Reviews

<table>
<thead>
<tr>
<th>Type</th>
<th>Author; Citation</th>
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<tbody>
<tr>
<td><strong>RT after BCS</strong></td>
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<tr>
<td>Individual patient data</td>
<td>Darby, 2011 [1]</td>
<td>RT after BCS. EBCTCG meta-analysis</td>
<td>Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials</td>
<td>• RT reduced the 10-y risk of first recurrence from 35.0% to 19.3% and reduced the 15-y risk of breast cancer death from 25.2% to 21.4%</td>
</tr>
</tbody>
</table>
• 5 trials, 3190 pts
• Small absolute decrease in risk of locoregional recurrence, no effect on OS |
• 3 meta-analyses by EBCTCG, 17 RCTs
• RT decreases local recurrence and death |
| **Hypofractionation**         |                  |                                            |                                                                      |                                                                                            |
| Meta-analysis                 | Budach, 2015 [40] | hypofractionation                         | Hypofractionated Radiotherapy as Adjuvant Treatment in Early Breast Cancer. A Review and Meta-Analysis of Randomized Controlled Trials | • PubMed (until 2014 based on included publications)
• 4 RCTs, 7085 pts with 10 y follow-up
• Recommend moderately hypofractionated RT after BCS in most pts |
| Meta-analysis                 | Zhou, 2015 [41]  | Hypofractionation vs conventional          | Systematic review and meta-analysis comparing hypofractionated with conventional fraction radiotherapy in treatment of early breast cancer | • MEDLINE, EMBASE, WEB OF SCIENCE, Cochrane Library and ClinicalTrials.gov up to August 2014
• Criteria: Hypofractionation should be more than 2.5 Gy per fraction, and total dose should no less than 23 Gy; conventional fractionation should be 1.8 or 2.0 Gy per fraction, and total dose more than 45 Gy.
• Included RCTs, concurrent controlled trials or retrospectively controlled trials. |
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<th>Comments</th>
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</thead>
</table>
| Systematic review       | Koukourakis, 2015 | Hypofractionation vs conventional WBI | Evidence based whole breast hypofractionated radiation therapy in patients with early breast cancer | • Included 23 studies (11 RCTs) of 15353 pts in review; 19 trials of 12,447 pts in meta-analysis  
• HFRT associated with decrease in grade 2/3 acute skin reactions; 2.5-3 Gy/fraction decreased photographic change while > 3 Gy/fraction increased; no significant difference in LRR, distant metastasis, OS, DFS, excellent/good cosmetic outcomes, symptomatic radiation pneumonitis, ischemic heart disease, symptomatic rib fracture  
• Conclude HFRT with 2.5-3.0 Gy/fraction is better choice |
| Meta-analysis            | James, 2010 [44]  | Fractionation size; Cochrane review/meta-analysis | Fraction size in radiation treatment for breast conservation in early breast cancer (Review) | • MEDLINE, Cochrane Central to May 2013: RCTs and meta-analyses  
• 4 RCTs: Canadian [42]); START A, START B, UK (Royal Marsden; Start Pilot) [43]  
• hypofractionation is as effective; more data about boost needed  
• Cochrane BC Registry, MEDLINE, Embase, WHO ICTPR to June 2009; reference lists, conferences  
• Included RCTs of unconventional vs conventional fractionation in women with BCS  
• 4 RCTS, 7095 pts  
• did not affect local recurrence, breast appearance, 5-y survival; decreased acute skin toxicity  
• Includes 2 new studies since previous version and altered the conclusions; longer-term follow-up is still required |
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<th>Type</th>
<th>Author; Citation</th>
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<th>Comments</th>
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<tbody>
<tr>
<td><strong>BOOST</strong></td>
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</tbody>
</table>
- 5 RCTs boost vs none all found improvement in local recurrence  
- 15 trials on boost technique  
- IMRT only for special cases e.g. IM nodes  
- IORT (ELIOT, x-rays)  
- fractionation  
- other |
| **IORT**                |                  |         |                                                                       |                                                                          |
- 6 non-RCT trials with IORT instead of EBRT tumour-bed boost  
- Targit A: need longer follow-up  
- ELIOT |
- Targit-A published after search but included  
- 3 Systematic reviews, 1 RCT (Targit-A), 10 case series  
- well-tolerated, low acute and late toxicity, no survival difference |
| **Partial breast irradiation** |                  |         |                                                                       |                                                                          |
| Meta-analysis           | Marta, 2015 [48,49] | APBI vs WBI | Accelerated partial irradiation for breast cancer: Systematic review and meta-analysis of 8653 women in eight randomized trials | - Cochrane Central 2014; MEDLINE to Feb 2014; Embase to July 2013; LILACS to Feb 2014; + reference lists  
- 8653 pts in 8 RCTs  
- Higher local recurrence with APBI, no |
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<th>Type</th>
<th>Author; Citation</th>
<th>Topic</th>
<th>Title</th>
<th>Comments</th>
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</thead>
</table>
| Meta-analysis | Lehman, 2014 [50] | BCS + PBI/APBI vs BCS + WBI | Partial breast irradiation for early breast cancer                   | - difference in OS, systemic or nodal recurrence  
- Are 7 ongoing RCTs comparing APBI vs WBI  
- European Brachytherapy Breast Cancer GEC-ESTRO Working Group (1170 pts)  
- National Surgical Adjuvant Breast and Bowel Project (NSABP)/Radiation Therapy Oncology Group (RTOG) trials (3000 pts): NSABP B39  
- NCT00818051 (ICI-IMPORT-HIGH)  
- NCT00814567 (ICI-IMPORT-LOW)  
- IRMA, NCT01803958  
- NCT00892814 (DBCCG PBI)  
- SHARE, NCT01247233   |
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<th>Type</th>
<th>Author; Citation</th>
<th>Topic</th>
<th>Title</th>
<th>Comments</th>
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</thead>
</table>
• RCTs comparing APBI vs WBI in early BC  
• 4 RCTs, 919 pts  
• Better cosmetic results; no difference in 5-y or 8-y OS, cancer specific survival, DFS, LR, contralateral BC, distant metastasis |
| Meta-analysis | Valachis, 2010 [53] | PBI vs WBI                | Partial breast irradiation or whole breast radiotherapy for early breast cancer: a meta-analysis of randomized controlled trials | • Cochrane Central, PubMed, ISI Web of Science until June 2008  
• RCTs comparing WBI vs limited filed or partial radiation after BCS; excluded trials with 2 different partial irradiation techniques or doses of same radiation technique  
• 3 trials of 1140 pts [54], [55,56], [57]  
• no difference in death, distant metastasis, supraclavicular recurrence; increased local and axillary recurrence |
• 7170 pts in 3 trials: MA.20, EORTC C22922-10925, and French trial  
• Additional regional RT to the internal mammary and medial supraclavicular LN statistically significantly  
• improved DFS, DMFS, and OS in stage I-III breast cancer |
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<th>Type</th>
<th>Author; Citation</th>
<th>Topic</th>
<th>Title</th>
<th>Comments</th>
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</thead>
</table>
| Meta-analysis       | Lv, 2015 [59]    | Internal mammary nodes                    | Efficacy of postoperative radiotherapy of internal mammary nodes in stage I–III breast cancer: A meta-analysis | • CNKI, CBM, Wanfang, PubMed, Embase, Web of Science, Cochrane (until 2013 based on included publications)  
• In Chinese so use only for trial identification  
• 7 trials involving 6835 pts  
• Stage I-III cancer  
• No difference in 5-y or 10-y survival |
| Timing              |                  |                                            |                                                                      |          |
• 3 trials (ARCOSEIN [60]; Arcangeli 2006 [61,62]; Bellon 2005 [63], 1166 pts)  
• No significant difference in OS, RFS, MFS. Concurrent chemoradiation increased anemia, telangiectasia, pigmentation and physician-reported assessment of cosmesis (but not by pts)  
• Older trials so do not assess RT and chemo; SECRAB was not yet published |
• 3 RCTs: ARCOSEIN [65-67], Arcangeli [61]; Rouesse [68] |
| Various             |                  |                                            |                                                                      |          |
| Systematic review   | Mukesh, 2012 [69] | PBI versus WBI Boost Fractionation         | Relationship between irradiated breast volume and late normal tissue complications: A Systematic review | • MEDLINE, Embase to 2011 (based on included publications)  
• Boost: EORTC 22881-10882  
• PBI: 4 trials complete (Christie, Yorkshire, Hungarian, TARGIT), others ongoing (ELIOT, IMPORT LOW, GEC-ESTRO, NSBP-39, RAPID, IRMA, DBCCG, SHARE) |

*Note: The table provides a summary of the literature on postoperative radiotherapy for early breast cancer, focusing on the timing of chemotherapy and radiotherapy, and the effectiveness of concurrent versus sequential approaches. The comments section highlights the key findings from various studies, including the number of trials, patient populations, and outcomes such as survival rates and side effects.*
<table>
<thead>
<tr>
<th>Type</th>
<th>Author; Citation</th>
<th>Topic</th>
<th>Title</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>Marta, 2011 [70]</td>
<td>Early stage breast cancer</td>
<td>Early stage breast cancer and radiotherapy: update</td>
<td>• MEDLINE, SciELO, Cochrane to 2010 (based on included publications)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and radiotherapy: update</td>
<td></td>
<td>• RT in BCS; RT in elderly pts with HT (CALGB)</td>
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<td></td>
<td></td>
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<td>• doses and fractionation, boost, APBI</td>
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<tr>
<td>Other issues</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>cancer after radiotherapy</td>
<td>A Systematic review and meta-analysis of 762,468 patients</td>
<td>• Found 13 studies; increased rates of second cancers, specifically lung,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for breast cancer</td>
<td></td>
<td>esophagus, sarcomas. Need normal tissue sparing RT techniques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>conformal RT</td>
<td>conformal irradiation of breast carcinomas</td>
<td>textbooks; data mainly from prospective non-randomized studies</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 14% incidence (4% high grade) of clinical radiation pneumonitis</td>
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<td></td>
<td></td>
<td>42% radiological radiation pneumonitis</td>
</tr>
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<td></td>
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<td></td>
<td>cancer in the elderly</td>
<td>• Clinical trial or meta-analysis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PRIME trial (note the PRIME II trial is now published as well)</td>
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</tbody>
</table>
## RCTs from 2009-2016

<table>
<thead>
<tr>
<th>Trial name/id</th>
<th>Author, Year Citation</th>
<th>Comparison</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td><strong>RT after BCS</strong></td>
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<tr>
<td>PRIME II</td>
<td>Kunkler, 2015 [74,75]</td>
<td>WBI vs none</td>
<td>Women with low-risk early breast cancer and endocrine treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=1326</td>
<td>At median 5 years: ipsilateral recurrence 1.3% vs 4.1%, p=0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-y OS 93.9% in both groups</td>
</tr>
<tr>
<td>SWeBCG 91RT</td>
<td>Lundstedt, 2010 [76] Malmstrom, 2010 [77] [abstract]</td>
<td>RT vs none</td>
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<tr>
<td></td>
<td></td>
<td>N=1187</td>
<td>Median 15 y follow-up</td>
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<tr>
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<td>RT did not affect OS: 70.8% vs 68.2%, p=0.79</td>
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<td>RFS improved: 62.6% vs 53.7%, p&lt;0.001</td>
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<td></td>
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<td></td>
<td>More long-term pain in RT group</td>
</tr>
<tr>
<td>BASO II</td>
<td>Blamey, 2013 [78]</td>
<td>2x2 design</td>
<td>RT vs wide local excision +/- tamoxifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=1135</td>
<td>LR: HR=0.37, p&lt;0.001 for RT vs wide local excision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Both tamoxifen and RT reduced recurrence, combined treatment to greater extent</td>
</tr>
<tr>
<td>RT 55-75</td>
<td>Tinterri, 2014 [79]</td>
<td>BCS +/- WBI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=749</td>
<td>IBR 3.4% vs 4.4%, ns</td>
</tr>
<tr>
<td>West Midlands Oncology Breast Cancer Group</td>
<td>Spooner, 2012 [80]</td>
<td>immediate RT (long 50 Gy in 25 daily fractions vs short 40 Gy in 15 daily fractions) vs delayed salvage treatment (no RT)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>N=707</td>
<td>Median 16.9 y follow-up</td>
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<td></td>
<td>First locoregional relapse 110 RT vs 161 no RT</td>
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<td>Any competing event HR 0.76 for RT vs no RT, p&lt;0.001</td>
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<tr>
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<td></td>
<td>Locoregional relapse reduced by 672% (HR=0.38, 95% CI 0.25-0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=636</td>
<td>Median follow-up 12.6 y</td>
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<tr>
<td></td>
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<td></td>
<td>Small improvement in LRR</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td>Toronto/British Columbia trial</td>
<td>Liu, 2015 [81]; Shi, 2012 [82]; Fyles, 2011, 2010 [83,84] [abstracts]; Fyles, 2004 [85]</td>
<td>Tamoxifen +/- RT</td>
<td>10-y OS 67% vs 66%, ns, N=501; n=769 in original publication Results by molecular subtype prognostic for IBR; hazard ratios comparing RT vs none given; RT is beneficial IBTR at 10 years: 5.0% WBI vs 13.8%</td>
</tr>
<tr>
<td>Uppsala/Orebro Breast Cancer Study Group</td>
<td>Wickberg, 2014 [86]</td>
<td>Sector resection +/- RT</td>
<td>N=381 20 y follow-up RT protects against recurrence during first 5 y</td>
</tr>
<tr>
<td>German Breast Cancer Study Group</td>
<td>Winzer, 2010 [87]</td>
<td>2x2 design RT (yes/no) and tamoxifen (yes/no)</td>
<td>N=361 (347 analyzed) Median 10 y follow-up EFS rate much higher with BCS only</td>
</tr>
<tr>
<td>Glasgow</td>
<td>McArdle, 2010 [88]</td>
<td>RT vs CMF vs RT + CMF</td>
<td>N=322 See McArdle 1986 for trial details [89] No difference in survival</td>
</tr>
<tr>
<td>Tampere and Helsinki Finland</td>
<td>Holli, 2009 [90] Holli, 2001 [91]</td>
<td>Pts with small tumor, wide tumor-free margin and axillary nodal dissection RT or not</td>
<td>N=264 Median 12.1 y follow-up Recurrence 11.6% vs 27.2%, p=0.0013 OS not significantly different (HR=0.63, p=0.11)</td>
</tr>
<tr>
<td>PRIME ISRCTN14817328</td>
<td>Williams, 2011 [92] Prescott, 2007 [93]</td>
<td>BCS + endocrine therapy +/- RT</td>
<td>N=255 QoL: RT associated with increased breast symptoms and fatigue, but lower insomnia and endocrine side effects shortly after treatment and up to 5 years; no difference in overall QoL</td>
</tr>
<tr>
<td>Various RCTs at Milan Cancer Institute</td>
<td>Demicheli, 2010 [94]</td>
<td>BCS +/- RT</td>
<td>IBTR 5.8% vs 24.5% at 10 years</td>
</tr>
</tbody>
</table>

**Hypofractionation**
<table>
<thead>
<tr>
<th>Trial name/id</th>
<th>Author, Year Citation</th>
<th>Comparison</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>START pilot</td>
<td>Yarnold, 2005 [95]</td>
<td>42.9 Gy in 13 fractions over 5 weeks vs 39 Gy in 13 fractions over 5 weeks vs 50 Gy over 25 factions in 5 weeks</td>
<td>N=1410&lt;br&gt;After minimum 5-y follow-up, risk of change in breast appearance was 45.7% (42.9 Gy) vs 30.3% (39 Gy) vs 39.6% (50 Gy)&lt;br&gt;Ipsilateral tumour relapse at median 9.7 y follow-up 9.6% (42.9 Gy) vs 14.8% (39 Gy) vs 12.1% (50 Gy)&lt;br&gt;Retrospective re-analysis of local recurrence vs new primary tumours</td>
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<td>Owen, 2006 [43]</td>
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<td>Gujral, 2011 [96]</td>
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<tr>
<td>START A</td>
<td>Start Trialists’ Group, 2008 [97]</td>
<td>13 fractions of 3.2 Gy vs 3.0 Gy (41.6 Gy or 39 Gy total) over 5 weeks vs 50 Gy in 25 fractions of 2.0 Gy</td>
<td>n=2236&lt;br&gt;After median 5.1 y follow-up, LRR 3.5% (41.6 Gy) vs 5.2% (39 Gy) vs 3.6% (50 Gy); lower later adverse effects after 39 Gy vs 50 Gy; breast appearance HR=0.69, p=0.01&lt;br&gt;At 5 y, adverse effects lower for 39 Gy than 50 Gy; rates were similar for 41.6 Gy and 50 Gy&lt;br&gt;After median 9.3 y, 10-y LRR 6.3% (41.6 Gy), 8.8% (39 Gy), 7.4% (50 Gy), p=0.65 (41.6 vs 50 Gy) and p=0.41 (39 Gy vs 50 Gy); moderate or marked breast induration, telangiectasia, edema less common in 39 Gy group than 50 Gy; these were not significantly different between 41.6 Gy and 50 Gy groups</td>
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<tr>
<td></td>
<td>Hopewood, 2010 [98]</td>
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<tr>
<td></td>
<td>Haviland, 2013 [99]</td>
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<tr>
<td>START B</td>
<td>Start Trialists’ Group, 2008 [100]</td>
<td>40 Gy in 15 F of 2.67 Gy over 3 weeks vs 50 Gy in 25 F of 2.0 Gy over 5 weeks</td>
<td>N=2215&lt;br&gt;Median 6.0 y follow-up: LRR at 5 y was 2.2% vs 3.3%; lower rates of late adverse effects with 40 Gy&lt;br&gt;At 5 y, adverse effects lower for 40 Gy than 50 Gy&lt;br&gt;Median 9.9 y follow-up: LRR 4.3% (40 Gy) vs 5.5% (50 Gy), p=0.21; breast shrinkage, telangiectasia, breast edema less common in 40 Gy group</td>
</tr>
<tr>
<td></td>
<td>Hopewood, 2010 [98]</td>
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</tr>
<tr>
<td></td>
<td>Haviland, 2013 [99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>START pilot, START</td>
<td>Yarnold, 2014</td>
<td>See individual trials:</td>
<td>No subgroups identified that disfavoured</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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</tr>
<tr>
<td>A, START B meta-analysis</td>
<td>[abstract]</td>
<td>hypofractionated vs standard fractionation</td>
<td>hypofractionation (patient age, breast size, tumour grade, axillary node status, type of surgery, cytotoxic chemotherapy, tumour bed boost and lymphatic radiotherapy) 40 Gy in 15 F is the UK standard since 2009</td>
</tr>
<tr>
<td>Canadian hypofractionation trial OCOG-1993-hypo</td>
<td>Arsenault, 2015 [101] [abstract] Bane, 2014 [102] Whelan, 2010 [42]</td>
<td>Hypofractionated (42.5 Gy in 16 fractions over 22 d) vs conventional WBI (50 Gy in 25 fractions over 35 d)</td>
<td>N=1234 main trial N=161 in acute toxicity study Acute skin toxicity less with hypofractionation, p&lt;0.001; better overall QoL N=989 for tumor factors; they did not predict response to hypofractionation Local recurrence at 10 y: 6.2% vs 6.7%, ns Good/Excellent cosmetic results: 69.8% vs 71.3%,ns Conclude hypofractionated not inferior</td>
</tr>
<tr>
<td>West Midlands Oncology Breast Cancer Group, UK</td>
<td>Spooner, 2012 [80]</td>
<td>immediate RT (long 50 Gy in 25 daily fractions vs short 40 Gy in 15 daily fractions) vs delayed salvage treatment (no RT)</td>
<td>N=707 Median 16.9 y follow-up First locoregional relapse 110 RT vs 161 no RT Any competing event HR 0.76 for RT vs no RT, p&lt;0.001 Locoregional relapse reduced by 67% (HR=0.38, 95% CI 0.25-0.53)</td>
</tr>
<tr>
<td>Cairo</td>
<td>Barsoum, 2010 [103] [104] [abstract, manuscript] Eissa 2010 [105] [thesis]</td>
<td>40 Gy in 15 fractions over 3 weeks (267 cGy /fraction) vs 50 Gy in 25 fractions over 35 days (200 cGy/fraction) RT given either concomitant or sequential to tamoxifen Pts &lt;50 y with BCS received boost of 1600 cGy in 8 fractions over 1.5</td>
<td>N=308 Maximum early skin reactions occurred in 2-3 week vs 5 week; no difference in late skin toxicity, cosmetic grades, cough, pulmonary fibrosis -4-y OS 84.8% vs 79.2%, p=0.408, locoregional DFS 97% vs 94.1%, p=0.265, DFS 75.7% vs 70.2%, p=0.248</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
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<tr>
<td><strong>FAST-Forward</strong></td>
<td>Zotova, 2015 [106] [abstract]</td>
<td>1 week vs 3 week schedule</td>
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</tr>
<tr>
<td>ISRCTN19906132</td>
<td>Brunt, 2016 [107] [after search date]</td>
<td>27 Gy in 5F of 5.4 Gy vs 26 Gy in 5 F of 5.2 Gy vs 40.05 Gy in 15 F of 2.67 Gy (control)</td>
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<td>Substudy opening in 2015: 627 pt receiving lymphatic radiotherapy + WBI</td>
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<td></td>
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<td>N=4110; 3200 plans collected so far and 2400 analyzed</td>
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<td>Report only of RT quality assurance and dose objectives for breast and organs at risk</td>
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<td>Follow-up ongoing for 10 y</td>
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<td>Skin toxicity substudies, n=190 and n=162</td>
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<tr>
<td></td>
<td></td>
<td>-in first substudy, grade 3 RTOG toxicity 13.6% (40 Gy) vs 9.8% (27 Gy) vs 5.8% (26 Gy)</td>
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<tr>
<td></td>
<td></td>
<td>-conclude acute breast skin reactions were mild</td>
<td></td>
</tr>
<tr>
<td><strong>UK FAST</strong></td>
<td>Tsang, 2012 [108,109]</td>
<td>five-fraction schedule WBI (28.5 Gy or 30 Gy in 5 once-weekly fractions of 5.7 Gy or 6.0 Gy) vs standard fractionation (50 Gy in 25 fractions)</td>
<td></td>
</tr>
<tr>
<td>ISRCTN62488883</td>
<td>FAST Trialists Group, 2011 [110]</td>
<td>N=915</td>
<td></td>
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<tr>
<td>CRUKE/04/015</td>
<td></td>
<td>95% of plans complied with protocol</td>
<td></td>
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<tr>
<td>NCT00814567</td>
<td></td>
<td>At 2 years post-randomization, no significant difference in breast appearance due to dose inhomogeneity</td>
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<tr>
<td></td>
<td></td>
<td>Photographic assessment at 2 y: mild/marked change risk 1.70 (p&lt;0.001) for 30 Gy vs 50 Gy and 1.15 (p=0.489) for 28.5 Gy vs 50 Gy</td>
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<td>3-y physician-assessed moderate/marked adverse effects 17.3% for 30 Gy (p&lt;0.001 vs 50 Gy), 11.1% for 28.5 Gy (p=0.18 vs 50 Gy), 9.5% for 50 Gy</td>
<td></td>
</tr>
<tr>
<td><strong>TomoBreast</strong></td>
<td>Versmessen, 2012 [111]</td>
<td>Hypofractionated tomotherapy (CT image guided IMRT; 42Gy in 15 fractions over 3 weeks + 15 x 0.6Gy/fraction boost if BCS) vs conventional RT(50Gy in 25 fractions over 5 weeks + 16Gy boost in 8 fractions if BCS)</td>
<td></td>
</tr>
<tr>
<td>NCT00459628</td>
<td>Verbanck, 2012 [112]</td>
<td>N=121</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adriaenssens, 2012</td>
<td>At 3 months post-RT, tomotherapy pts had better improvement in global health status and role- and cognitive-functioning, faster recovery from fatigue</td>
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<td>Total lung capacity was significantly decreased and ventilation heterogeneity was significantly increased 3 months after baseline in the CR arm, but not in the TT arm</td>
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<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td>RTOG 1005</td>
<td>Khan, 2013 [114] [abstract]</td>
<td>15x2.67 Gy (40 Gy) WHI + 15x0.53 Gy concurrent boost (48 Gy) vs 25x2 Gy (50 Gy) + sequential boost of 7x2 Gy</td>
<td>Skin toxicity grade &gt;1 at 2 y was 30% tomotherapy vs 60% conventional</td>
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<td></td>
<td></td>
<td></td>
<td>N=2354</td>
</tr>
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<td></td>
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<td>Started 2011, ongoing</td>
</tr>
<tr>
<td>DBCG HYPO</td>
<td>Haislund, 2012 [115] [Abstract]</td>
<td>40 Gy/15F WBI vs 50 Gy/25F</td>
<td>N=976</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ongoing</td>
</tr>
<tr>
<td>New York, NY</td>
<td>Ishaq, 2015 [116] [abstract]</td>
<td>WBI plus daily (0.5 Gy) or weekly (2 Gy) tumour bed boost</td>
<td>N=400</td>
</tr>
<tr>
<td></td>
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<td>Studied effect of time of day RT received</td>
<td>No time of day differences in fatigue or toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear what was randomized</td>
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<tr>
<td>NCT01266642</td>
<td>Shaitelman, 2015 [117]</td>
<td>Hypofractionated (42.56 Gy/16 fractions + boost) vs conventionally fractionated WBI (50 Gy/25 fractions + boost)</td>
<td>N=287</td>
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<td></td>
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<td>Lower rates of acute toxic effects, less fatigue</td>
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<td></td>
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<td>Follow-up ongoing</td>
</tr>
<tr>
<td></td>
<td>Hou, 2015 [118]</td>
<td>43.2 Gy to the whole breast in 18 fractions for 24 days with a concomitant boost (50.4 Gy) to the tumor bed. The control group received 45 Gy to the whole breast in 25 fractions for 44 days with a boost to the tumor bed of 59 Gy</td>
<td>N=80</td>
</tr>
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<td></td>
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<td></td>
<td>Shortened schedule is as effective for local control, survival, adverse skin reactions, cosmetic outcome</td>
</tr>
<tr>
<td></td>
<td>B.P. Koirala Memorial Cancer Hospital, Bharatpur, Nepal</td>
<td>42.5 Gy/16F/22 days vs 50 Gy/25F/35days. Patients who underwent BCS received additional lumpectomy boost 10Gy/5F/1wk</td>
<td>N=80</td>
</tr>
<tr>
<td></td>
<td>Karmacharya, 2012 [119] [abstract]</td>
<td></td>
<td>No significant difference in acute skin toxicity or radiation pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Hashemi, 2012 [120] [English abstract]</td>
<td>42.5 Gy in 16 F vs 50 Gy in 25F</td>
<td>N=52</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No differences in skin complications or cosmetic results</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td>Frąkancrca-Nixon, 2011</td>
<td>43.2 Gy/16F/22d + boost vs 50 Gy/25F/5w + boost</td>
<td>N=25&lt;br&gt;Ongoing&lt;br&gt;Cardiac function study</td>
<td></td>
</tr>
<tr>
<td>SGW (St George and Wollongong)</td>
<td>45 Gy in 25 fractions WBI + 16 Gy in 8 fractions electron boost vs 50 Gy in 25 fractions</td>
<td>N=688&lt;br&gt;No difference in pt/clinician cosmetic assessment; panel rated boost arm better; conclude negative cosmetic effect of boost offset by lower WBI&lt;br&gt;-colour change [122], exploratory QoL, long-term adverse effects [123]&lt;br&gt;-primary outcome of local failure not yet reported&lt;br&gt;At median 8.5 y follow-up, 10-y in breast local failure rate 9.7% vs 5.1%, p=0.047</td>
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</tr>
<tr>
<td>Young Boost Trial</td>
<td>High boost (26 Gy) vs std low boost (16 Gy); 50 Gy WBI in both</td>
<td>N=2421&lt;br&gt;Young pts, BCS&lt;br&gt;At 4 y, cosmetic outcome better in low boost&lt;br&gt;Primary outcome of recurrence not reported</td>
<td></td>
</tr>
<tr>
<td>EORTC-22881-10882-ROG-BCG</td>
<td>50 Gy WBI in all pts&lt;br&gt;• 15-16 Gy boost (patients with microscopically complete resections) vs no boost</td>
<td>N=5318&lt;br&gt;20-y follow-up: OS 59.7% vs 61.1%, ns; ipsilateral breast recurrence 12% vs 16.4%, p&lt;0.0001; severe fibrosis 5.2% vs 1.8%, p&lt;0.0001&lt;br&gt;-cosmetic outcome: worse with boost at 3 years, fibrosis ongoing until at least 9 years&lt;br&gt;N=1616 in subset with central pathology review&lt;br&gt;Boost reduced local relapse rate, p=0.0006, HR=0.47&lt;br&gt;Local relapse 11.4% vs 19.4%, p=0.0046, HR=0.51 for pts &lt;50 y and 8.6% vs 18.9% for high grade invasive</td>
<td></td>
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<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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</tbody>
</table>
|               | Poortmans, 2009 [130] | 10 Gy vs 25-26 Gy boost (pts with microscopically incomplete resections) | ductal carcinoma  
N=251 [130]  
Microscopically incomplete group: no difference in local control or survival, fibrosis more frequent with high boost |
|               | Uwini, 2009 [131]    | Portion of data from EORTC (simulation-based treatment plan) and Young Boost (CT-scan-based) trials | N=1331  
dose in CT-scan planning significantly higher |
|               | Rajan, 2014 [132]    | Compare modalities of boost (16 Gy in 8 fractions) following WBI: electron beam vs photon (3DCRT) | N=50  
slightly increased acute skin toxicity with 3DCRT photon but better dosimetrically  
similar skin, subcutaneous toxicity and cosmetic scores at 2 y; 1 locoregional failure in each arm |
|               | Cooper, 2014 [133]   | Prone WBI: daily vs weekly boost | N=401  
Median 36 m follow-up: better cosmetic outcomes with weekly boost  
-3 local recurrence in weekly group, 1 in daily  
-RFS similar |
|               | Millar, 209 [134]    | BCT +/- boost | N=498  
-results by molecular subtype but not treatment |

**IMRT vs RT**

|                | Coles, 2016 [135] [abstract] |  
- 40 GY/15F to whole breast (control)  
- 36 Gy/15F whole breast and 40Gy/15F to partial breast (test 1)  
- 40 Gy/15F to partial breast (test 2) | N=2018  
Median follow-up 68.3 months  
5-y LR 1.1% vs 0.2% vs 0.5%; conclude PBI non-inferior to WBI  
10-y LR in oral presentation (not in abstract)  
Overall trial end date 2019 |
<table>
<thead>
<tr>
<th>Trial name/id</th>
<th>Author, Year Citation</th>
<th>Comparison</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPORT HIGH (CRUK/06/003) NCT00818051 ISRCTN47437448</td>
<td>Tsang, 2015 [136] Donovan, 2015 [137] [editorial]</td>
<td>N=2568 (planned ?) -clinical impact of trial [136]</td>
<td></td>
</tr>
<tr>
<td>IMPORT -IGRT (a substudy of IMPORT HIGH)</td>
<td></td>
<td></td>
<td>N=218, observational design</td>
</tr>
<tr>
<td>Cambridge IMRT</td>
<td>Mukesh, 2014, 2013 [138] [139] Barnett, 2012 [140] [141]</td>
<td>Forward planned field-in-field IMRT (simple IMRT) vs std RT 1145 pts evaluated; those with dose inhomogeneity were randomized</td>
<td>N=815 Longitudinal study on effect on PROMS compared to std RT at 5 y -at 5 y, PROMS did not demonstrate benefit of simple IMRT over std RT -at 5 y, fewer pts in IMRT group developed suboptimal overall cosmesis and skin telangiectasia</td>
</tr>
<tr>
<td>IMRT-MC2 NCT01322854</td>
<td>Krug, 2014 [142] [abstract]</td>
<td>3D-conformal tangential RT + sequential boost vs inverse-planned IMRT with a simultaneous integrated boost</td>
<td>Interim results of first 109 pts Primary endpoints are locoregional control and cosmetic outcome Similar cosmetic results, both had significant deterioration at 6 weeks</td>
</tr>
<tr>
<td>RTOG 1005 NCT01349322</td>
<td>Chen, 2015 [143]</td>
<td>Hypofractionated WBI + boost vs std WBI + sequential boost</td>
<td>Treatment planning: IMRT allows slightly better dose uniformity and/or normal tissue sparing -Ongoing, no publications of outcomes</td>
</tr>
<tr>
<td>IORT</td>
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<tr>
<td>TARGIT-A NCT00983684</td>
<td>Vaidya, 2014 [144,145]</td>
<td>Risk-adapted RT using TARGIT(single dose targeted intraoperative RT) vs WBI (external beam, EBRT)</td>
<td>N=3451 Supplemental EBRT in 15.2%</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td>ISRCTN 34086741</td>
<td>Keshtgar, 2013 [146][abstracts]</td>
<td>-supplemental EBRT (excluding boost) for TARGIT pts if unforeseen adverse features on final pathology</td>
<td>5-y risk of local recurrence in conserved breast 3.3% TARGIT vs 1.3% EBRT, p=0.042</td>
</tr>
<tr>
<td></td>
<td>Others publications [145,147-157]</td>
<td></td>
<td>Breast cancer mortality similar (2.6% vs 1.9%, p=0.56), fewer non-breast-cancer deaths (1.4% vs 3.5% due to fewer cardiovascular causes and other cancers Less grade 3/4 skin complications with TARGIT Superior cosmetic results with TARGIT</td>
</tr>
<tr>
<td>TARGIT-B</td>
<td>Vaidya, 2010 [158]</td>
<td>Pts at high risk of local recurrence: Tumor bed boost with TARGIT vs EBRT; WBI in both groups</td>
<td>Study announcement, no results</td>
</tr>
<tr>
<td>ELIOT NCT01849133</td>
<td>Veronesi, 2013 [159]</td>
<td>Whole breast external RT (50 Gy + 10 Gy boost)or intraoperative RT with electrons (ELIOT)(21Gy single dose)</td>
<td>N=1305 Medan 5.8 y follow-up: 35 pts ELIOT vs 4 pts external had IBTR (p&lt;0.0001); 5-y IBRT 4.4% ELIOT vs 0.4%; 5-y OS 96.8% vs 96.9% Fewer skin side effects with ELIOT, p=0.0002</td>
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<tr>
<td>Partial breast irradiation</td>
<td></td>
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<tr>
<td>GEC-ESTRO APBI trial NCT00402519</td>
<td>Strnad 2016, 2013 [164,165]</td>
<td>APBI vs WBI + boost</td>
<td>N=1193 Both well tolerated with moderate early side effects; less acute dermatitis, more hematoma,</td>
</tr>
<tr>
<td>GEC-ESTRO BREAST WG PHASE III MULTICENTRIC APBI TRIAL</td>
<td></td>
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<td>Late side effects (1 y): less Grade 1/2 skin toxicity , other effects no difference At 5 y: local recurrence 1.44% vs 0.92%, p=0.42; late skin effects 3.2% vs 5.7%, p0.08; subcutaneous tissue effects 7.6% vs 6.3%, p=0.53 -difference below relevance margin of 3%; APBI is not inferior for 5-y local control, DFS, OS</td>
</tr>
<tr>
<td>Florence NCT02104895</td>
<td>Meattini, 2015, 2016 [166,167] Livi, 2015 [168]</td>
<td>APBI with IMRT vs external WBI</td>
<td>N=520 5-y OS 99.4% vs 96.6%, APBI had better acute, late, and cosmetic outcome</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td>(Budapest, Hungary)</td>
<td>Polgar, 2013, 2014 [55,169]</td>
<td>PBI vs WBI</td>
<td>&gt;age 70 subgroup (n=117)</td>
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<tr>
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<td>PBI either by 7.5.2Gy HD multicatheter brachytherapy or 50 Gy electron beam (not randomized)</td>
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<td>N=258</td>
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<tr>
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<td></td>
<td>10-y results: LR, OS, CSS, DFS similar; better cosmetic results with PBI</td>
</tr>
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<td>More skin side effects, telangiectasia with electrons, but less fat necrosis compared to HD-PBI</td>
</tr>
<tr>
<td>(Barcelona, Spain)</td>
<td>Rodriguez, 2013 [170]</td>
<td>APBI vs WBI</td>
<td>N=102</td>
</tr>
<tr>
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<td></td>
<td>No local recurrence at 5 years in either group, no difference in survival</td>
</tr>
<tr>
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<td>APBI less acute side effects and lower radiation dose to healthy tissue</td>
</tr>
<tr>
<td>NSABP B-39</td>
<td>Julian, 2011 [171] [abstract]</td>
<td>PBI (intracavitary brachytherapy vs MammoSite or other single-entry intracavitary device vs 3-d conformal APBI vs WBI</td>
<td>N=4216, follow-up ongoing</td>
</tr>
<tr>
<td>RTOG 0413</td>
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<tr>
<td>NCT00103181</td>
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<tr>
<td>IRMA</td>
<td>Valli, 2012 [172]</td>
<td>PBI (38.5 Gy in 10 fractions, 2x/day for 5 d) vs WBI (50 Gy in 25 fractions, 1xday)</td>
<td>N=3302; to Feb 2016 n=2484 Ongoing</td>
</tr>
<tr>
<td>NCT01803958</td>
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<tr>
<td>SHARE</td>
<td>Belkacemi, 2013 [173]</td>
<td>APBI (1 wk, using 3D conformal RT) vs standard RT (WBI + boost) vs hypofractionated RT (3 wk)</td>
<td>N=2800 (planned); n=1006 actual Note: may be changed to 2 arms (APBI vs other) Follow-up ongoing, no data</td>
</tr>
<tr>
<td>French UNICANCER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trial</td>
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<tr>
<td>NCT01247233</td>
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<tr>
<td>SHARE</td>
<td>Olivotto, 2013 [174]</td>
<td>3D-CRT APBI vs WBI</td>
<td>N=2135</td>
</tr>
<tr>
<td></td>
<td>Peterson, 2015 [175]</td>
<td></td>
<td>Primary outcome IBTR but too few events yet</td>
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<td>Worse cosmesis and increased toxicities with APBI</td>
</tr>
<tr>
<td>DBCG PBI</td>
<td>Haislund, 2012 [115]</td>
<td>40 Gy/15F PBI vs WBI</td>
<td>N=882</td>
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<tr>
<td>NCT00892814</td>
<td></td>
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<td>Ongoing</td>
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<td>Primary endpoint late radiation morbidity (fibrosis),</td>
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<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
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<tr>
<td><strong>Nodes: ALND vs RT</strong></td>
<td></td>
<td></td>
<td>secondary endpoints other late morbidity, recurrence</td>
</tr>
<tr>
<td>AMAROS EORTC 10981-22023</td>
<td>Donker, 2014 [176,177]</td>
<td>ALND vs axillary radiotherapy</td>
<td>n=1425 SN+ Comparable axillary control; less lymphedema with ART</td>
</tr>
<tr>
<td>NCT00014612</td>
<td></td>
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<tr>
<td>OTOASOR</td>
<td>Savolt, 2016 [178] [abstract] Savolt, 2013 [179] [Hungarian]</td>
<td>Completion ALND vs axillary nodal irradiation if SLN+</td>
<td>N=2106 pts. ANI without cALD does not increase risk of axillary failure</td>
</tr>
<tr>
<td></td>
<td>Bing, 2016 [180] Bing, 2015 [181] [abstract]</td>
<td>N+ pts were randomized to axillary node sampling + AXRT vs axillary node clearance</td>
<td>N=321 (855 in 2 trials, including N0 pts not randomized to RT) Median follow-up 19.4 y Similar breast cancer survival: HR=1.07, p=0.69; more axillary recurrence in pt with sampling + AXRT, HR=2.64, p=0.05; no metastasis-free survival difference HR=1.03, p=0.85</td>
</tr>
<tr>
<td>ISRCTN54765244</td>
<td>Goyal, 2015 [182] [abstract]</td>
<td>Standard care plus axillary clearance or axillary RT</td>
<td>N=1900 planned Recruiting</td>
</tr>
<tr>
<td><strong>Nodes: WBI +/- nodal irradiation</strong></td>
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<tr>
<td>EORTC 22922 NCT00002851</td>
<td>Poortmans, 2015 [183] Matzinger, 2010 [184]</td>
<td>WBI +/- (internal mammary and medial supraclavicular lymph node irradiation)</td>
<td>N=4004 76% BCS, rest mastectomy Median 10.9 y follow-up: 10-y OS 82.3% nodal irradiation vs 80.7% control, p=0.06; DFS 72.1% vs 69.1%, p=0.04; DDFS 78.0% vs 75.0%, p=0.02; breast cancer mortality 12.5% vs 14.4%, p=0.02 Acute side effects were modest; lung toxicities increased with nodal treatment (4.3% vs 1.3%, p&lt;0.0001, but no difference in performance status</td>
</tr>
<tr>
<td>MA.20</td>
<td>Whelan, 2015 [185]</td>
<td>WBI +/- regional nodal irradiation</td>
<td>N=1832</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
<td>Other</td>
</tr>
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<tr>
<td>NCT00005957</td>
<td>Whelan, 2010 [186]</td>
<td>Pts node positive or high-risk node negative cancer</td>
<td>Median 9.5 y follow-up; OS 82.8% vs 81.8%, p=0.38; DFS 82.0% vs 77.0%, p=0.01; grade 2+ acute pneumonitis 1.2% vs 0.2%, p=0.01, lymphedema 8.4% vs 4.5%, p=0.001</td>
</tr>
<tr>
<td>GRISO 053</td>
<td>Zurrida, 2013 [187]</td>
<td>Breast RT +/- Axillary RT</td>
<td>N=435 Retrospectively assessed prognostic importance of biological factors 10-y incidence of distant metastases 1% vs 7%, p=0.037 In pts with high Ki67, DFS better with axillary RT, p=0.005</td>
</tr>
<tr>
<td></td>
<td>Lissidini, 2014 [188]</td>
<td>breast RT 50 Gy in 25 fractions, designed to minimize axilla irradiation</td>
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<tr>
<td></td>
<td>See Veronesi, 2005 [189] for 5-y data</td>
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<tr>
<td>UK-ANZ POSNOC</td>
<td>Goyal, 2015 [190]</td>
<td>Systemic therapy + RT to breast/chest wall if indicated: randomize to adjuvant therapy alone vs adjuvant therapy + axillary node clearance or axillary radiotherapy</td>
<td>N=1900 planned Ongoing</td>
</tr>
<tr>
<td>Tunio, 2015 [191]</td>
<td>Chest wall/breast +/- supraclavicular RT</td>
<td></td>
<td>N=40 Hyperthyroidism 15% vs 5%, p&lt;0.001; risk can be minimized by shielding during RT</td>
</tr>
<tr>
<td>NSABP B-51 RTOG 1304</td>
<td>Mamounas, 2015 [192]</td>
<td>BCS + WBI +/- regional nodal radiotherapy</td>
<td>N=1636 planned; N=96 to date of publication Credentialing of treatment planning still required for several institutions</td>
</tr>
<tr>
<td></td>
<td>Leif, 2015 [193]</td>
<td></td>
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<tr>
<td>KROG 08-06</td>
<td>Chung, 2015 [194]</td>
<td>RT including or excluding internal mammary lymph nodes</td>
<td>N=747 planned Reported on dosimetric differences to IMN</td>
</tr>
<tr>
<td>Timing with chemo or surgery</td>
<td></td>
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<tr>
<td>CO-HO-RT</td>
<td>Bourgier, 2016 [8]</td>
<td>Concurrent vs sequential RT</td>
<td>N=150</td>
</tr>
<tr>
<td>Trial name/id</td>
<td>Author, Year Citation</td>
<td>Comparison</td>
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<tr>
<td>SECRAB ISRCTN84214355 NCT00003893</td>
<td>Fernando, 2014, 2012, 2011, 2010 [197-200] [abstracts]</td>
<td>Sequential vs synchronous chemoradiation using CMF or anthracycline-CMF</td>
<td>N=2296 Reduced local recurrence after synchronous treatment: 2.8% vs 5.1%, p=0.03 Cosmesis assessed in 382 pts: no difference Increase in acute skin toxicity and telangiectasia in synchronous group</td>
</tr>
<tr>
<td>Pinnaro, 2011 [62]</td>
<td>CMF plus concurrent vs sequential RT</td>
<td>N=206 No difference in 10-y DFS, MFS, OS, recurrence</td>
<td></td>
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<tr>
<td>Zhang, 2014 [201] [abstract]</td>
<td>Concomitant vs sequential anastrozole + RT</td>
<td>N=80 No significant differences</td>
<td></td>
</tr>
<tr>
<td>Abd El-Bary, 2010 [202] [abstract]</td>
<td>Concomitant vs sequential aromatase inhibitor with RT</td>
<td>N=40 No statistically significant differences in adverse events, local recurrence, distant metastasis [but trial very small]</td>
<td></td>
</tr>
<tr>
<td>Cooper, 2015 [203] [abstract]</td>
<td>Prone WBI + daily (0.5 Gy) vs weekly (2 Gy) boost</td>
<td>N=1000 (planned); 415 to date Primary endpoint acute toxicity: similar in both arms</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


11. Members of the Breast Cancer Disease Site Group. Breast irradiation in women with early stage invasive breast cancer following breast conserving surgery. Program in


192. Mamounas EP, Bandos H, White JR, Julian TB, Khan AJ, Shaitelman SF, et al. NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) will reduce invasive cancer events in patients (pts) with positive axillary (Ax) nodes who are ypN0 after neoadjuvant chemotherapy (NC). Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).


OUTCOMES DEFINITION

1. EDUCATION AND INFORMATION - A document in EDUCATION AND INFORMATION is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “EDUCATION AND INFORMATION”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY - A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.