Radiation Therapy in the Management of Breast Cancer

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KEYWORDS

- Breast cancer
- Radiation therapy
- Ductal carcinoma in situ
- Breast-conserving therapy
- Postmastectomy irradiation

KEY POINTS

- Adjuvant radiation therapy (RT) after wide local excision (WLE) for ductal carcinoma in situ (DCIS) reduces the relative risk of ipsilateral breast tumor recurrence (IBTR) at 10 years by 54%. The addition of tamoxifen (TAM) to RT further decreases the cumulative incidence of IBTR as well as contralateral recurrence.

- Six randomized trials established the equivalence of breast-conserving therapy (BCT) (breast-conserving surgery [BCS] followed by RT) and mastectomy on overall survival in patients with early-stage breast cancer at 20-year follow-up. The addition of RT to BCS decreased the 10-year risk of local recurrence by 16%, which translated into a 15-year reduction in the risk of breast cancer death by 4%.

- Alternative methods of irradiation for early-stage breast cancer have been developed, to abbreviate treatment times, enhance convenience, and/or decrease exposure to the normal tissues. These methods include hypofractionated therapy, prone breast irradiation, and accelerated partial breast irradiation (APBI). A large phase III trial comparing the efficacy of APBI versus whole-breast irradiation (WBI) is underway.

- According to the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis, postmastectomy irradiation (PMRT) proportionally decreased the risk of locoregional recurrence (LRR) by 73% in node-positive patients. This finding translated into an increase in breast cancer-specific survival at 15 years by 5.4%.

INTRODUCTION

Radiation therapy plays an essential role in the management of breast cancer by eradicating subclinical disease after surgical removal of grossly evident tumor. Radiation reduces local recurrence rates and increases breast cancer–specific survival in patients with early-stage breast cancer after BCS and in node-positive patients who have undergone mastectomy.¹ This article reviews the following topics: (1) the rationale for...
adjuvant RT and the evidence for its use in noninvasive and invasive breast cancer, (2) RT delivery techniques for breast-conserving therapy such as hypofractionated RT, partial breast irradiation, and prone irradiation, and (3) indications for PMRT.

**DUCTAL CARCINOMA IN SITU**

The efficacy of radiation in reducing local recurrence in DCIS has been demonstrated by 4 randomized trials comparing outcomes in patients who received lumpectomy plus RT versus lumpectomy alone (Table 1). In 2010, the EBCTCG published a meta-analysis including more than 3000 women with DCIS treated in 4 of these trials. Radiation was found to reduce the relative risk of IBTR at 10 years by 54% (absolute reduction 15.2%, \( P < .00001 \)) in all patients. A significant reduction in the risk of local recurrence was seen, regardless of the age at diagnosis, margin status, and differences in tumor characteristics such as size, grade, and multifocality. The use of RT did not significantly affect breast cancer–related mortality.

To investigate the benefit of adding hormonal therapy to patients receiving radiation, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial randomized 1804 women with DCIS treated with lumpectomy and RT to TAM versus placebo between 1991 and 1994. At 15 years, the addition of TAM to RT decreased the cumulative incidence of IBTR from 10.0% (RT + placebo) to 8.5% (\( P = .025 \)). The addition of TAM is equally effective in preventing contralateral breast cancer recurrence, with a 15-year cumulative incidence of 10.8% in patients who received RT and placebo versus 7.3% in patients who received RT and TAM (\( P = .023 \)).

Although adjuvant RT after lumpectomy for DCIS has been shown to improve local control in all subsets of patients, it remains controversial whether or not patients with low-risk characteristics require treatment, as the toxicities of treatment may potentially

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Accrual Dates</th>
<th>Patients Enrolled (n)</th>
<th>Median Follow-up (yr)</th>
<th>Radiation Therapy Dose</th>
<th>Relative Risk Reduction in IBTR in RT Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>1985–1990</td>
<td>818</td>
<td>17.3</td>
<td>50 Gy in 2 Gy fractions (^{a})</td>
<td>DCIS = 47% Invasive disease = 52%</td>
</tr>
<tr>
<td>EORTC 10853</td>
<td>1986–1996</td>
<td>1010</td>
<td>10.4</td>
<td>50 Gy in 2 Gy fractions (^{b})</td>
<td>DCIS = 48% Invasive disease = 42%</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>1987–1999</td>
<td>1067</td>
<td>8.4</td>
<td>50 Gy in 2 Gy fractions or 48 Gy in 2.4 Gy fractions or 54 Gy in 2 Gy fractions</td>
<td>DCIS = 67% Invasive disease = 41%</td>
</tr>
<tr>
<td>UK/ANZ DCIS</td>
<td>1990–1998</td>
<td>1030</td>
<td>12.7</td>
<td>50 Gy in 2 Gy fractions</td>
<td>DCIS = 38% Invasive disease = 32%</td>
</tr>
</tbody>
</table>

**Abbreviations**: EORTC, European Organisation for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; SweDCIS, Swedish Breast Cancer Group DCIS trial; UK/ANZ DCIS, United Kingdom, Australia, and New Zealand DCIS trial.

\(^{a}\) Nine percent of patients randomized to lumpectomy + radiation therapy received boost.

\(^{b}\) Five percent of patients randomized to lumpectomy + radiation therapy received boost.
outweigh the benefits. In 2006, Wong and colleagues investigated whether WLE alone was adequate in treating small \( \leq 2.5 \text{ cm mammographically} \) grade 1 to 2 DCIS with negative margins (defined as absence of DCIS \( \geq 1 \text{ cm from the inked margin} \)). The use of chemotherapy or TAM was not permitted in this trial. At 5 years, the cumulative IBTR rate was 12.5%. Given the high rate of local recurrence, the trial was terminated early. Investigators concluded that WLE alone was not sufficient for local control, even in patients with favorable histology. In 2009, the Eastern Cooperative Oncology Group published the results of a prospective trial of 701 women with DCIS treated with WLE alone. Surgical microscopic margins were required to be 3 mm or more. Patients were categorized into low-risk (low or intermediate histologic grade DCIS \( 2.5 \text{ cm or smaller} \)) versus high-risk groups (high-grade DCIS \( 1 \text{ cm or smaller} \)). Median follow-up was 6.2 years. Although the low-risk women had acceptably low IBRT rates (6.1%) at 5 years, patients in the high-risk group had a 15.3% rate of IBTR at 5 years, suggesting that excision alone was inadequate as sole therapy in this patient subset.

EARLY-STAGE BREAST CANCER

Breast-Conserving Therapy

To date, 6 prospective randomized trials comparing BCT with mastectomy have been performed. Although patient selection criteria and length of follow-up between these trials differed, all 6 trials established the equivalence of BCT and mastectomy on survival outcomes. Two of the largest trials with 20 years follow-up include the NSABP B-06 and Milan trials. NSABP B-06 included 1851 women with invasive tumors that were 4 cm or less and randomized to total mastectomy, lumpectomy alone, or lumpectomy with postoperative WBI. Negative margins were required and defined as no tumor at the inked margin. At 20 years, the LRR rate in the mastectomy group was 14.8%, versus 17.5% in the lumpectomy alone group and 8.1% in the lumpectomy followed by postoperative RT group. Local failure in this study was defined by recurrence in the chest wall or scar, but ipsilateral breast failure in patients who underwent lumpectomy was not considered as local failure. No significant differences in disease-free survival, distant-disease-free survival, or overall survival were observed among groups who underwent mastectomy and BCT. Similar results were reported by the Milan Cancer Institute trial. At 20 years, the rate of death from all causes was 41.7% in the BCT cohort and 41.2% in the mastectomy cohort \((P = 1.0)\), demonstrating that the long-term survival rate with BCT is equivalent to mastectomy.

Multiple randomized trials have demonstrated that the addition of RT to the whole breast after BCS significantly reduces local relapse. With a median follow-up of 20 years, the NSABP B-06 trial demonstrated that the cumulative incidence of IBTR in women who underwent BCS alone was 39% versus 14% \((P<.001)\) for women who received RT after BCS. The long-term survival impact of this reduction in local control was recently published by the EBCTCG group, who conducted a meta-analysis that included 10,801 women in 17 randomized trials of RT versus no RT after BCS. The addition of RT was found to reduce the 10-year risk of any first recurrence from 35% to 19%. This benefit in local control translated into a 15-year reduction in the risk of breast cancer death from 25% to 21%. These benefits were observed across all patients, regardless of nodal status. For patients with node-negative disease, adjuvant RT reduced any recurrence by 15.4% \((95\% \text{ confidence interval [CI]}, 13.2–17.6; P<.00001)\) and improved survival by 3.3% \((95\% \text{ CI}, 0.8–5.8; P = .005)\). For patients with node-positive disease, adjuvant RT reduced any recurrence by reduction 21.2% \((95\% \text{ CI}, 14.5–27.9; P<.00001)\) and improved survival by 8.5% \((95\% \text{ CI}, 1.8–15.2; P = .01)\). Overall, 1 breast cancer death was avoided for every 4 local recurrences prevented by the addition of RT.
## Table 2
### Phase III trials comparing breast-conserving therapy and mastectomy

<table>
<thead>
<tr>
<th></th>
<th>IGR</th>
<th>Milan</th>
<th>NSABP B-06</th>
<th>NCI</th>
<th>EORTC 10801</th>
<th>DBCG-82TM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible patients (n)</td>
<td>179</td>
<td>701</td>
<td>1211</td>
<td>237</td>
<td>868</td>
<td>793</td>
</tr>
<tr>
<td>Eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor (cm)</td>
<td>≤2</td>
<td>≤2</td>
<td>≤4</td>
<td>≤5</td>
<td>≤5</td>
<td>Not specified</td>
</tr>
<tr>
<td>Axilla</td>
<td>cN0-1a, Nb</td>
<td>cN0</td>
<td>cN0-1</td>
<td>cN0-1</td>
<td>Apex pN0 (optional)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Age (y)</td>
<td>&lt;70</td>
<td>≤70</td>
<td>No age limit</td>
<td>No age limit</td>
<td>≤70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Surgery</td>
<td>Modified radical M vs Tumorectomy + Ax + RT</td>
<td>Halsted M vs Quad + Ax + RT</td>
<td>Total M + Ax vs Lump + Ax + RT</td>
<td>Modified radical M vs Lump + Ax + RT</td>
<td>Modified radical M vs Lump + Ax + RT</td>
<td>Modified radical M vs Lump + Ax + RT</td>
</tr>
<tr>
<td>Boost</td>
<td>15 Gy</td>
<td>10 Gy</td>
<td>No boost</td>
<td>10–20 Gy</td>
<td>25 Gy</td>
<td>10–25 Gy</td>
</tr>
<tr>
<td>Median follow-up (y)</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LR (BCT vs M)</td>
<td>13% vs 18%</td>
<td>9% vs 2%</td>
<td>3% vs 10%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22% vs 0%</td>
<td>20% vs 12%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5% vs 7%</td>
</tr>
<tr>
<td>P</td>
<td>.44</td>
<td>P&lt;.001</td>
<td>No analysis</td>
<td>No analysis</td>
<td>P = .01</td>
<td>P = .16</td>
</tr>
<tr>
<td>OS (BCT vs M)</td>
<td>73% vs 65%</td>
<td>59% vs 58%</td>
<td>46% vs 47%</td>
<td>54% vs 58%</td>
<td>65% vs 66%</td>
<td>58% vs 51%</td>
</tr>
<tr>
<td>P</td>
<td>.19</td>
<td>1.0</td>
<td>.23</td>
<td>.67</td>
<td>.11</td>
<td>.20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Local failure was defined by recurrence in the chest wall or scar.

<sup>b</sup> Locoregional recurrence.

Abbreviations: Ax, axillary dissection; c/pN, clinical/pathologic nodal stage; DBCG, The Danish Breast Cancer Cooperative Group; IGR, Institut Gustave-Roussy Breast Cancer Group; LR, local recurrence; Lump, lumpectomy; M, mastectomy; NCI, National Cancer Institute; OS, overall survival; Quad, quadrantectomy; other abbreviations same as Table 1.
The aforementioned trials are important for understanding the context in which the rationale for irradiation after BCS was derived. Over time, local control rates with whole-breast RT after BCS have continued to improve, reflecting changes in pathologic analysis of surgical margins, increased use of systemic therapy, and improvements in imaging, surgical, and RT techniques.

**Selection Criteria for BCT**

Contraindications to RT in the setting of BCT are categorized as absolute or relative. Absolute contraindications include pregnancy, inability to obtain negative margins, multicentric cancer, or diffuse malignant-appearing calcifications. Relative contraindications include a history of prior RT and collagen vascular disease (CVD). Mastectomy remains the standard of care in patients who experience an in-breast recurrence after BCT. However, the feasibility of re-irradiation with APBI for select patients with small, recurrent breast cancer is currently being investigated in a Radiation Therapy Oncology Group (RTOG) trial.22 RT can also be offered on a case-by-case basis to patients with CVD, with the caveat that these patients may be at enhanced risk of soft tissue fibrosis and subcutaneous toxicities after treatment. Data identifying patients with breast cancer and CVD who are at the greatest risk of RT-induced toxicity is limited to single-institution series. In a retrospective analysis of 209 patients with CVDs treated with RT to various sites, rheumatoid arthritis (RA) was not found to be associated with an elevated risk of late toxicity, while systemic lupus erythematosus (SLE) and scleroderma were associated with increased late RT toxicity.23 To date, there is only 1 matched case-control study investigating BCT in the setting of active CVDs.24 Thirty-six patients with CVDs (RA 47%, SLE 14%, scleroderma 11%, Raynaud phenomenon 11%, polymyositis 11%, and Sjögren disease 6%) and their double matched controls with respect to age, RT technique, systemic therapy, histologic features, and treatment dates were identified. No significant difference was found between patients with CVDs and control group patients in acute toxicity (14% vs 8%, \( P = .40 \)). At the median follow-up of 12.5 years, a significant increased risk of late complication was found in patients with CVDs (17% vs 3%, \( P < .001 \)); however, in subset analysis based on specific CVD, the statistically significant difference was noted only in patients with scleroderma.

**Use of a Boost**

The rationale for adding a boost to the tumor bed after WBI for invasive breast cancer was established by the European Organization for the Research and Treatment of Cancer (EORTC) 22881-10882 trial.25 This trial included 5318 women age 70 years or less with T1-2N0-1M0 breast cancer who received WLE and whole-breast RT (50 Gy) and were randomized to a boost to the lumpectomy cavity (16 Gy) or observation. All patients were required to have a 1-cm margin of macroscopically normal breast tissue. At a median follow-up of 10.8 years, a local relapse rate of 10.2% (95% CI, 8.7%–11.8%) was observed in the no boost versus 6.2% (95% CI, 4.9%–7.5%) in the boost cohort (\( P < .0001 \)).26 Although a proportional risk reduction in local recurrence of 39% was seen across all age groups, the absolute reduction in local recurrence with boost was the largest in patients 40 years or younger (from 23.9% to 13.5%, \( P = .0014 \)). Based on these results, a boost after whole-breast RT is most frequently used in women younger than 60 years with invasive breast cancer or in the setting of close or positive margins. Indications for boost in older women or in those with DCIS are less well defined, given the lack of data demonstrating a local control benefit in these subgroups.3,4,25
**Omission of RT in Elderly Women with T1N0 Estrogen Receptor–Positive Breast Cancer**

Select patient groups have been identified as having a low risk of local recurrence after BCS without RT. Two randomized trials evaluated the incremental value of RT in older women with small, node-negative, estrogen receptor (ER)-positive tumors treated with BCS and hormonal therapy. The Cancer and Leukemia Group B (CALGB) conducted a trial of 636 women who were 70 years or older and underwent BCS and TAM for ER-positive, T1N0 disease. Patients were randomized to RT versus observation. The 5-year LRR rate was significantly lower in patients who received RT (1% vs 4% in no RT, \( P < .001 \)). Updated results with longer follow-up (median 10.2 years) were reported, demonstrating a 2% local recurrence rate in the RT + TAM versus 9% in the TAM alone arm. There was no significant difference in the rates of mastectomy for local recurrence, distant metastases, or overall survival between the 2 groups.

A second trial from Canada published in parallel with the CALGB study had an identical design but broader inclusion criteria. This study randomized 769 women 50 years or older with T1-2N0 breast cancer treated with BCS and TAM/RT. At 5 years, the addition of RT significantly reduced the rate of local recurrence (0.6% vs 7.7% in the TAM only cohort, \( P < .001 \)).

The local control rates demonstrated in the patients who did not receive RT in these trials are considered acceptable to warrant the omission of RT in women 70 years or older with small, node-negative, ER-positive breast cancer who plan on receiving hormonal therapy. Patient preference, ability to tolerate hormonal therapy, treatment goals, and competing comorbidities are all important factors to be considered when making this decision.

**Techniques of Breast Irradiation**

A standard course of RT to the whole breast consists of 50 to 50.4 Gy delivered in 25 to 26 fractions, followed by a 10- to 16 Gy boost to the tumor bed. Several alternative methods of radiation delivery have been developed, all with the purpose of abbreviating treatment times, enhancing convenience, and/or decreasing exposure to the normal tissues. Each technique and fractionation schema should be individualized to the patient’s anatomy, tumor characteristics, and availability of institutional resources.

**Hypofractionation**

Hypofractionation (HFx) is defined as the delivery of larger-than-standard doses of radiation over a shorter period of time. A concept originally conceived in the 1960s, HFx was initially associated with a high rate of late complications, therefore resulting in abandonment of its use. As the understanding of the radiobiologic principles that govern normal tissue responses improved, HFx regimens regained popularity in the United States. To date, there have been 3 randomized trials that have established equivalent local control and cosmetic outcomes between HFx and standard fractionation (SFx) regimens.

The most influential among these trials is the one conducted by the Ontario Clinical Oncology Group. This study included 1234 women with node-negative invasive breast cancer who received WLE and axillary node dissection, randomized to SFx (25 treatments over 5 weeks) or HFx RT to the whole breast. The HFx arm consisted of 16 treatments using a higher dose per day—a regimen now commonly used in the United States and referred to as the “Canadian fractionation.” With a median follow-up of 12 years, there was no significant difference in local recurrence (6.7% for the standard fractionated group vs 6.2% for the HFx group) or cosmesis (71.3% of women in the standard fractionation group vs 69.8% of women in the HFx group had good or excellent cosmetic outcome).
These results were corroborated by the Standardization of Breast Radiotherapy (START) A and B trials from the United Kingdom, which tested various HFx regimens against SFx in women with both node-negative and node-positive breast cancer. The START A trial included 2 different HFx schedules: 41.6 Gy delivered in 13 fractions over 3 weeks and 39 Gy delivered in 13 fractions over 3 weeks. With a median follow-up of 5.1 years, the LRR rates were equivalent in the SFx cohort (3.6%) and the 41.6 Gy HFx cohort (3.5%), whereas the 39 Gy HFx group demonstrated a significantly higher local recurrence rate (5.2%). The START B trial compared SFx to a HFx regimen of 40 Gy delivered in 15 fractions over 3 weeks. With a median follow-up of 6 years, the HFx group demonstrated a lower but not statistically significant recurrence rate (2.2%) compared with the SFx arm.

Despite the uniformity of the results, several differences in patient selection, length of follow-up, and use of systemic therapy and boost RT among the 3 trials should be noted (Table 3). In the Canadian trial, most patients had tumors with low-risk features (T1-2, grade 1–2, and ER+), none of the patients received boost RT, only 10.9% of patients received adjuvant systemic therapy, and women with large breast separations (ie, very thick breasts) were excluded. In contrast, the START A and B trials included patients with larger tumors and node-positive disease, 36% of patients received adjuvant systemic therapy, and there was no exclusion criteria based on breast size. Moreover, the use of a boost was not standardized, information on hormonal receptors status was unavailable, and the median follow-up was short.

These differences have precluded the widespread acceptance of HFx regimens into practice in the United States. In an effort to formalize guidelines on selection criteria for HFx RT, the American Society of Therapeutic Radiology and Oncology (ASTRO) published a consensus statement issued by a panel of experts in 2010. The group agreed that HFx RT was appropriate in patients who met all the following criteria:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Randomized trials of hypofractionation for whole-breast irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (n)</td>
<td>Canadian Trial</td>
</tr>
<tr>
<td></td>
<td>1234</td>
</tr>
<tr>
<td>Stage</td>
<td>T1-2 pN0</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>12 y</td>
</tr>
<tr>
<td>Surgery type</td>
<td>All BCS</td>
</tr>
<tr>
<td>Hypofractionation regimen</td>
<td>42.5 Gy/16 fx over 3 wk</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>11% chemotherapy (CMF)</td>
</tr>
<tr>
<td>Use of boost</td>
<td>None</td>
</tr>
<tr>
<td>Exclusion criteria based on breast size</td>
<td>Excluded &gt;25 cm</td>
</tr>
<tr>
<td>Regional nodal irradiation</td>
<td>None</td>
</tr>
<tr>
<td>Receptor status</td>
<td>Majority were ER+/PR+</td>
</tr>
</tbody>
</table>

Abbreviations: CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; PR, progesterone receptor; T, tumor stage; other abbreviations same as Table 2.

age 50 years or older at diagnosis, pathologic stage T1-T2 N0 disease treated with BCS, no chemotherapy, and a radiation plan with 7% dose inhomogeneity. A consensus on the applicability of HFx to young patients and those who received chemotherapy and boost was unable to be reached, based on the lack of mature clinical data on these patient subsets.

**Prone breast irradiation**

Standard tangential WBI in the supine position with standard fractionation was the predominant position used in the seminal trials of both conventional and HFx RT. Prone positioning was developed in the early 1990s as an alternative treatment of women with large breasts, with the goal of decreasing toxicities resulting from increased breast thickness, dose inhomogeneity, and the presence of skin folds.

The prone position requires patients to lie with the treated breast suspended through an aperture in the breast board, which displaces the breast away from the chest wall (Fig. 1). In single-institution series, prone RT has been shown to deliver a lower radiation dose to the lung and heart without compromising tumor control. One disadvantage of this technique is the lesser coverage of level I and II axillary lymph nodes. Other suboptimal candidates for prone RT include patients with tumors near the chest wall or elderly or obese patients who are unable to tolerate the position.

**Accelerated partial breast irradiation**

APBI has gained significant popularity as a radiation technique in women opting for BCT. APBI delivers larger-than-standard doses of daily radiation to the postsurgical cavity plus a 1- to 2-cm margin over 1 to 2 weeks, therefore lowering RT exposure to normal tissues and expediting overall treatment times. The rationale for APBI is that most local recurrences after BCT occur in the immediate vicinity of the original tumor. Prospective randomized trials comparing lumpectomy with or without postoperative RT have shown that 80% to 90% of local recurrences are located at the site of

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**Fig. 1.** Prone irradiation. (Adapted from Setton J, Cody H, Tan L, et al. Radiation field design and regional control in sentinel lymph node-positive breast cancer patients with omission of axillary dissection. Cancer 2012;118:1994–2003; with permission.)
lumpectomy\textsuperscript{20,38,39} whereas the rate of “elsewhere failures” at sites far removed from the tumor bed were 4%, which approaches the risk for developing contralateral breast cancer. Pathologic studies have also shown that tumor cells rarely extend 4 cm beyond the index lesion in patients who underwent mastectomy without an extensive intraductal component.\textsuperscript{40} Taken together, these results suggest that RT offers the highest local control benefit when doses are directed to the tumor bed.

APBI can be administered with a variety of methods including multicatheter brachytherapy (MIB), intracavitary balloon brachytherapy such as MammoSite (Hologic Inc., Bedford, MA, USA), intraoperative RT (IORT), and external beam conformal therapy (EBRT) (\textbf{Fig. 2}). Each of these techniques has its own unique advantages and disadvantages, emphasizing the importance of individualizing the technique to patient anatomy, preferences, and resources. Data from modern randomized trials comparing WBI and APBI have just become available, or trials are actively accruing patients (\textbf{Table 4}).\textsuperscript{41–47} The largest among these trials is the NSABP B-39/RTOG 0413,\textsuperscript{42} which is aiming to accrue 4300 patients and permits APBI with MIB, EBRT, or MammoSite. By enrolling patients with all grades of DCIS, invasive cancers with 1 to 3 positive lymph nodes, and ER-negative breast cancers, this trial will provide data on the efficacy of APBI in a higher-risk population of patients than those included in prior studies.

MIB represents the APBI technique with the longest follow-up. The ability to differentially load multiple catheters throughout the tumor bed allows for the greatest dosing flexibility.\textsuperscript{48,49} However, it is an invasive procedure and requires considerable training and expertise, which limits use of this technique. In contrast, intracavitary brachytherapy is the most popular form of APBI currently used in the United States. This technique involves placement of a balloon-based catheter applicator within the lumpectomy cavity, which is subsequently inflated to securely fit against the cavity. Postoperatively, the balloon is filled with saline, and a high dose rate brachytherapy (HDR) afterloading device inserts an iridium-192 source into the center of the balloon. The

\textbf{Fig. 2.} Four methods of accelerated partial breast irradiation delivery.
radiation dose is prescribed to a 1 cm distance from the balloon surface. Treatment is delivered over a total of 10 fractions, twice a day over 5 consecutive days. Compared with MIB, it is easier to perform and less invasive. The MammoSite Registry Trial, a prospective study by the American Society of Breast Surgeons, represents the largest body of evidence for patients treated with this technique. Among the 1449 patients enrolled, the actuarial IBTR rate was 3.8% at 5 years and 90.6% of patients demonstrated good/excellent cosmesis.50

IORT consists of a single dose of RT administered to the operative bed at the time of lumpectomy. It is the most convenient to deliver of all the APBI techniques but is limited by lack of availability of centers in the United States equipped to perform this treatment. Another disadvantage is the lack of knowledge of final margin pathology and lymph node status before treatment delivery. Interest in IORT was renewed by the publication of the Targeted Intraoperative Radiotherapy for Breast Cancer trial,45 in which 2232 women 45 years or older were randomized to receive either WBI or IORT after WLE using a single dose of 20 Gy delivered to the tumor bed using a device called INTRABEAM (Carl Zeiss, Oberkochen, Germany), a miniature x-ray source that delivers a point source of orthovoltage x-rays. Most patients had node-negative, low- or intermediate-grade invasive tumors 2 cm or less. Fourteen

Table 4
Modern phase III trials of APBI versus WBI

<table>
<thead>
<tr>
<th>Institution/Trial</th>
<th>Total n/Target Accrual (y)</th>
<th>Control Arm</th>
<th>Experimental Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Institute of Oncology EIO</td>
<td>1200 (2000–2007)</td>
<td>WBI 50 Gy in 25 fx ± 10 Gy Boost</td>
<td>IORT (21 Gy in 1 fx)</td>
</tr>
<tr>
<td>European Brachytherapy Breast Cancer GEC-ESTRO Working Group</td>
<td>1170 (2004–2009)</td>
<td>WBI 50–50.4 Gy in 25–28 fx + 10 Gy Boost</td>
<td>Brachytherapy only 32.0 Gy 8 fx HDR or 30.3 Gy 7 fx HDR or 50 Gy pulsed dose rate</td>
</tr>
<tr>
<td>Medical Research Council—UK IMPORT LOW</td>
<td>1935 (2007–2010)</td>
<td>WBI 2.67 Gy × 15 fx</td>
<td>WBI 2.4 Gy × 15 PBI 2.67 Gy × 15 PBI only 2.67 Gy × 15</td>
</tr>
<tr>
<td>Ontario Clinical Oncology Group Canadian Trial RAPID</td>
<td>2128 (2006–2011)</td>
<td>WBI ± 10 Gy boost: 42.5 Gy in 16 fx for small breasts or 50 Gy in 25 fx for large breasts</td>
<td>3D-CRT only (38.5 Gy in 10 fx)</td>
</tr>
<tr>
<td>NSABP B-39/ RTOG 0413</td>
<td>Accrual goal: 4300 (2005–present)</td>
<td>WBI 50–50.4 Gy ± 10–16 Gy Boost</td>
<td>MIB (34 Gy in 10 fx) or MammoSite (34 Gy in 10 fx) or 3D-CRT (38.5 Gy in 10 fx)</td>
</tr>
</tbody>
</table>

Abbreviations: GEC-ESTRO, The Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology; IMPORT LOW, Intensity Modulated and Partial Organ Radiotherapy trial; RAPID, Randomized Trial of Accelerated Partial Breast Irradiation; TARGIT, Targeted Intraoperative Radiotherapy for Breast Cancer trial; other abbreviations same as Table 1.
percent of patients in the IORT group received additional WBI if final pathology revealed prespecified high-risk features. At 4 years, the local recurrence rates were equivalent between both groups (1.2% in IORT vs 0.95% in WBI, \( P = .41 \)), as was the incidence of major toxicity (3.3% in IORT vs 3.9% in WBI, \( P = .44 \)). Criticisms of this trial include the short follow-up (median 4 years) and the potential for low therapeutic efficacy of a single dose delivered to the distant margins of the target volume.

EBRT is the most common technique used for APBI in the NSABP/RTOG trial.\(^{42}\) Compared with other APBI techniques, its advantages include its noninvasive nature, excellent dose homogeneity, availability, and ease of use. The first randomized trial comparing WBI and APBI using EBRT was conducted at Christie Hospital (Manchester, UK) between 1982 and 1987.\(^{51}\) A total of 708 patients with invasive ductal or lobular carcinoma measuring 4 cm or less were included. All patients received lumpectomy without axillary dissection. Microscopic evaluation of the surgical margins was not performed, and chemotherapy was not administered. At 8 years, the in-breast recurrence rate was significantly higher in the APBI arm compared with the WBI arm (25% vs 13%, \( P < .0001 \)). In retrospect, the high local recurrence rates were attributed to poor patient selection, outdated RT techniques, inadequate management of the axilla, lack of systemic therapy, and incomplete pathologic examination of margins. With radiation technique and technological advancements, the ability to visualize the target cavity and to deliver adequate dose consistently and precisely with external beam therapy have improved. One of the prospective studies with the longest follow-up using modern EBRT APBI technique was conducted at the William Beaumont Hospital.\(^{52}\) In this study, 94 patients with stage 0–II breast cancer with lesions 3 cm or less, negative margins, and negative nodes were treated with 3-dimensional conformal RT to the tumor bed at 3.85 Gy per fraction to a total of 38.5 Gy. At a median follow-up of 4.2 years, the investigators reported 1.1% IBTR, demonstrating with appropriate RT technique and patient selection, EBRT APBI can achieve adequate local control.

At present, data on long-term outcomes with APBI and the best technique for its delivery are limited. Recognizing that mature results from randomized trials will not be available for some time, the ASTRO Task Force developed a consensus statement to help guide patient selection for the practice of APBI outside of a clinical trial. Patients who were “suitable,” “cautionary,” or “unsuitable” for APBI performed off-protocol were defined. The last 2 groups were defined based on lack of data to support treatment of these subsets, rather than known lack of efficacy or toxicities (Table 5).\(^{34}\) It is important to acknowledge that these guidelines are subject to evolve as further data become available.

**POSTMASTECTOMY IRRADIATION**

PMRT is used to treat regions that are at risk for local and regional recurrence but are not excised during modified radical mastectomy, such as the chest wall lymphatics and upper axillary, supraclavicular, and internal mammary lymph nodes. The most influential study to establish the efficacy of PMRT in node-positive patients comes from the Early Breast Cancer Trialists Collaborative Group Overview, a meta-analysis that included more than 9000 patients from randomized trials of RT after mastectomy plus varying extent of axillary surgery. In this meta-analysis, PMRT was found to proportionally decrease the risk of LRR by 73% (annual odds ratio 0.28), with the 5-year risk of local recurrence of 5.8% versus 22.8% in node-positive patients treated with and without PMRT. This reduction in LRR translated
Three randomized trials of PMRT contributed most patients included in the EBCTCG meta-analysis and represent the first PMRT trials to have routinely used modern radiotherapy techniques and systemic therapy and report long-term follow-up. These include the Danish 82b and 82c and Vancouver British Columbia trials. Three of these trials, the Danish trials, were performed simultaneously from

### Table 5

<table>
<thead>
<tr>
<th>Factors</th>
<th>Suitable Group: Suitable for APBI if all Criteria are Present</th>
<th>Cautionary Group: Any of These Criteria Should Involve Concern When Considering PBI</th>
<th>Unsuitable Group: Unsuitable for APBI Outside a Clinical Trial if Any of These Criteria Are Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age (y)</td>
<td>&gt;60</td>
<td>50–59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>BRCA 1/2 mutation</td>
<td>Not present</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>Pathologic Tumor size (cm)</td>
<td>≤2</td>
<td>2.1–3.0</td>
<td>3</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>T0 or T2</td>
<td>T3–4</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative by at least 2 mm</td>
<td>Close (&lt;2 mm)</td>
<td>Positive</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVSI</td>
<td>Not present</td>
<td>Limited/focal</td>
<td>Extensive</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
<td>Negative</td>
<td>—</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Unicentric only</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size ≤2 cm</td>
<td>Clinically unifocal with total size 2.1–3.0 cm</td>
<td>In microscopically multifocal &gt;3 cm in total size or if clinically multifocal</td>
</tr>
<tr>
<td>Histology</td>
<td>Favorable subtypes</td>
<td>Invasive lobular</td>
<td>—</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
<td>≤3 cm</td>
<td>If &gt;3 cm in size</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nodal</td>
<td>pN0 (i, i+)</td>
<td>—</td>
<td>pN1, pN2, pN3</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SN Bx or ALND</td>
<td>—</td>
<td>None performed</td>
</tr>
<tr>
<td>Treatment</td>
<td>Neoadjuvant therapy</td>
<td>—</td>
<td>If used</td>
</tr>
</tbody>
</table>

Abbreviations: ALND, axillary lymph node dissection; BRCA, breast cancer; LCIS, lobular carcinoma in situ; LVSI, lymphovascular space involvement; SN Bx, sentinel node biopsy; other abbreviations same as Tables 1–5.


into a 5.4% benefit in 15-year breast cancer–specific survival and a 4.4% benefit in overall survival.¹
1982 to 1989. Danish 82b included 1705 premenopausal women who received cyclo-
phosphamide, 5-fluorouracil, and methotrexate (CMF). Danish 82c recruited 1375
postmenopausal patients who received TAM. The 18-year rates of LRR (with or
without simultaneous distant metastases) were 49% and 14% in the control and
PMRT arms, respectively.56 In a subsequent subgroup analysis of patients who had
greater than 8 lymph nodes dissected, the 15-year overall survival was 29% and
39% in the control and PMRT groups, respectively.57

The British Columbia Cancer Agency trial, which was conducted between 1976 and
1985, randomized 318 premenopausal women with node-positive breast cancer to RT
or observation after mastectomy. All patients received CMF chemotherapy. With
a median of 20 years of follow-up, the addition of PMRT resulted in improved LRR-
free survival (74% control vs 90% PMRT), breast cancer–specific survival (38%
control vs 53% PMRT) and overall survival (37% control vs 47% PMRT).55

Despite their importance in establishing the efficacy of PMRT, several caveats to
these trials must be considered when using these data to formulate current practice
guidelines. In all 3 trials, rates of locoregional failure in the control arms were higher
than would be expected with standard axillary dissection. The Danish trial had a low
median number of axillary lymph nodes removed,7 which may have contributed to
high axillary failure rates and also limit detailed analysis of patient subgroups with 1
to 3 lymph nodes.

**PMRT in 1 to 3+ Lymph Nodes**

It is well accepted that PMRT is standard in patients with 4 or more involved axillary
lymph nodes, primary tumors greater than 5 cm with any number of positive nodes,
or any T4 tumors, based on consistent LRR rates of 15% or greater in these
subgroups.58–60 Indications for PMRT in patients with 1 to 3 positive lymph nodes
are more controversial, as this patient subgroup carries a lower risk of LRR.

The British Columbia trial, the combined 2 Danish trials, and the EBCTCG meta-
analyses that includes all 3 trials demonstrated a similar proportional survival benefit
of PMRT for women with 1 to 3 or 4 or more positive lymph nodes.1,55,57 In the EBCTCG
meta-analysis, the “benefit ratio” of reduced breast cancer–specific mortality was
0.4 for patients with 1 to 3 and 0.21 for 4 or more positive nodes. However, the afore-
mentioned limitations of these studies have prevented routine extrapolation of these
recommendations to the 1 to 3 positive node patient group. Moreover, the EBCTCG
meta-analysis included trials that used outdated radiotherapy techniques, had limited
or no information on prognostic factors such as histologic grade and lymphovascular
invasion, and did not distinguish between trials that did and did not use systemic
therapy.

Several large retrospective studies have examined the combined effect of clinical
and pathologic variables in subsets of 1 to 3 nodes positive who have not received
PMRT.61–63 Based on these results, factors such as patient age, tumor grade, tumor
size, receptor status, extranodal extension, margin status, and lymphovascular inva-
sion are used by clinicians to assess the risk of LRR in patients with 1 to 3+ nodes and
thereby guide recommendations for PMRT. Gene expression profiling to predict the
risk of locoregional failure (LRF) after mastectomy has been studied by a group in
Taiwan, who found that a 34-gene model segregated groups of patients into 2 cate-
gories: those with a 3-year LRR of 32% and another with no LRRs.64 Although prom-
ising, this approach requires significant validation before it can be used to tailor
treatment recommendations.

Prospective data on the use of PMRT in this subgroup are forthcoming from
the Selective Use of Postoperative Radiotherapy after Mastectomy trial, which
randomizes high-risk node-negative or 1 to 3 node-positive patients who underwent mastectomy to PMRT or observation. In the meantime, all patients with 1 to 3 positive nodes should have an informed discussion with a radiation oncologist regarding the benefits and risks of treatment.

REFERENCES


57. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007;82:247–53.


