Breast Cancer Treatment Guidelines

These guidelines are based on the Breast Cancer Treatment (PDQ®)–Health Professional Version by the National Cancer Institute (PDQ® Adult Treatment Editorial Board, 2025).

Surgical treatment for breast cancer

Operable breast cancer requires a multimodal approach to treatment. After the presence of a malignancy is confirmed by biopsy, the following surgical treatment options can be discussed with the patient before a therapeutic procedure is selected:

- Breast-conserving surgery.
- Modified radical mastectomy (removal of the entire breast with axillary dissection of levels I and II) with or without breast reconstruction.

To guide the selection of neoadjuvant or adjuvant therapy, many factors including stage, grade, and molecular status of the tumor (e.g., estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor type 2 receptor [HER2], or triple-negative status) are considered.

Surgical staging of the primary tumor

Selection of a local therapeutic approach depends on the following factors:

- Location and size of the lesion.
- Analysis of the mammogram and/or magnetic resonance imaging or additional imaging.
- Breast size.
- Patient’s desire to preserve the breast.

Options for surgical management of the primary tumor include:

- **Breast-conserving surgery (with consideration of radiation therapy).** All histological types of invasive breast cancer may be treated with breast-conserving surgery plus radiation therapy. However, the presence of inflammatory breast cancer, regardless of histological subtype, is a contraindication to breast-conserving therapy. The presence of multifocal disease in the breast and a history of collagen vascular disease are relative contraindications to breast-conserving therapy. Prior radiation to the breast was previously considered a contraindication to breast-conserving surgery. However, research has increasingly shown that repeat radiation therapy may be feasible and safe in select patient populations.
- **Mastectomy with or without breast reconstruction.**

Survival is equivalent with any of these options, as documented in the EORTC-10801 trial and other prospective randomized trials. Also, a retrospective study of 753 patients who were divided into three groups based on hormone receptor status (ER positive or PR positive; ER negative and PR negative but HER2 positive; and triple negative) found no differences in disease control within the breast in patients treated with standard breast-conserving surgery; however, there are not yet substantive data to support this finding.

The rate of local recurrence in the breast after conservative treatment is low and varies slightly with the surgical technique used (e.g., lumpectomy, quadrantectomy, segmental mastectomy, and others). Whether completely clear microscopic margins are necessary has been debated. However, a multidisciplinary consensus panel recently used margin width and ipsilateral breast tumor recurrence

from a meta-analysis of 33 studies (N = 28,162 patients) as the primary evidence base for a new consensus regarding margins in patients with stage I and stage II breast cancer treated with breast-conserving surgery plus radiation therapy. Results of the meta-analysis include the following:

- Positive margins (ink on invasive carcinoma or ductal carcinoma *in situ*) were associated with a twofold increase in the risk of ipsilateral breast tumor recurrence compared with negative margins.
- More widely clear margins were not found to significantly decrease the rate of ipsilateral breast tumor recurrence compared with no ink on tumor. Thus, it was recommended that the use of no ink on tumor be the new standard for an adequate margin in invasive cancer.
- There was no evidence that more widely clear margins reduced ipsilateral breast tumor recurrence for young patients or for those with unfavorable biology, lobular cancers, or cancers with an extensive intraductal component.

For patients undergoing partial mastectomy, margins may be positive after primary surgery, often leading to re-excision. A clinical trial of 235 patients with stage 0 to III breast cancer who underwent partial mastectomy, with or without resection of selective margins, randomly assigned patients to have additional cavity shave margins resected (shave group) or not (no-shave group). Patients in the shave group had a significantly lower rate of positive margins than those in the no-shave group (19% vs. 34%, $P = .01$) and a lower rate of second surgery for clearing margins (10% vs. 21%, $P = .02$).

Axillary lymph node management

Axillary node status remains the most important predictor of outcome in patients with breast cancer. The axillary lymph nodes are staged to aid in determining prognosis and therapy.

Sentinel lymph node (SLN) biopsy is the initial standard axillary staging procedure performed in women with invasive breast cancer. The SLN is defined as any node that receives drainage directly from the primary tumor, allowing for more than one SLN, which is often the case. Studies have shown that the injection of technetium Tc 99m-labeled sulfur colloid, vital blue dye, or both around the tumor or biopsy cavity, or in the subareolar area, and subsequent drainage of these compounds to the axilla results in the identification of the SLN in 92% to 98% of patients. These reports demonstrate a 97.5% to 100% concordance between SLN biopsy and complete axillary lymph node dissection (ALND). SLN biopsy alone is associated with less morbidity than axillary lymphadenectomy.

Evidence (SLN biopsy):

1. ALMANAC, a randomized trial of 1,031 women compared SLN biopsy followed by ALND when the SLN was positive with ALND in all patients.

   Quality of life at 1 year (as assessed by the frequency of patients experiencing a clinically significant deterioration in the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Breast scale) was superior in the SLN biopsy group (23% deteriorating in the SLN biopsy group vs. 35% in the ALND group; $P = .001$). Arm function was also better in the SLN group.

2. The National Surgical Adjuvant Breast and Bowel Project's (NSABP-B-32 [NCT00003830]) multicenter, phase III trial randomly assigned women (N = 5,611) to undergo either SLN plus ALND or SLN resection alone. ALND was only performed if the SLNs were positive.

   The study showed no detectable difference in overall survival (OS), disease-free survival (DFS), and regional control. The OS rate was 91.8% for SLN plus ALND versus 90.3% for SLN resection alone ($P = .12$).

Because of the following trial results, ALND is unnecessary after a positive SLN biopsy in patients with limited SLN-positive breast cancer treated with breast conservation or mastectomy, radiation therapy, and systemic therapy.

Evidence (ALND after a positive SLN biopsy in patients with limited SLN-positive breast cancer):

1. ACOSOG Z0011 (Alliance, NCT00003855), a phase III, noninferiority, multicenter, randomized clinical trial, evaluated whether ALND is required after a positive SLN biopsy. Women were randomly assigned to undergo ALND or no further axillary treatment. Patients had clinical T1 or T2 invasive breast cancer without palpable adenopathy and one to two SLNs containing metastases identified by frozen section. All patients underwent lumpectomy, tangential whole-breast radiation therapy, and appropriate systemic therapy. OS was the primary end point, and DFS was the secondary end point. Because of enrollment challenges, a total of 891 women out of a target enrollment of 1,900 women were randomly assigned to one of the two treatment arms.
    - At a median follow-up of 6.3 years, the 5-year OS rate was 91.8% (95% confidence interval [CI], 89.1%–94.5%) with ALND and 92.5% (95% CI, 90.0%–95.1%) with SLN biopsy alone.
    - Detailed analysis of the radiation field design found that 15% of patients also received treatment to the supraclavicular region (in addition to standard tangents). Of those with detailed radiation records available for review, 43 patients (18.9%) received regional nodal radiation therapy.
    - The 5-year DFS rate was 82.2% (95% CI, 78.3%–86.3%) with ALND and 83.9% (95% CI, 80.2%–87.9%) with SLN biopsy alone.
2. In a similarly designed trial (IBCSG 23-01), 929 women with breast tumors smaller than 5 cm and SLN involvement smaller than 2 mm were randomly assigned to ALND or no ALND.
    - Patients without axillary dissection had fewer DFS events (hazard ratio [HR], 0.78; 95% CI, 0.55–1.11).
    - No difference in OS was observed.
3. The AMAROS trial (NCT00014612) studied ALND and axillary radiation therapy after identification of a positive SLN.
    - ALND and axillary radiation therapy provided excellent and comparable axillary control for patients with T1 or T2 primary breast cancer and no palpable lymphadenopathy who underwent breast-conserving therapy or mastectomy.
    - The use of axillary radiation therapy was also associated with significantly less morbidity.

For patients who require an ALND, the standard evaluation usually involves only a level I and II dissection, thereby removing a satisfactory number of nodes for evaluation (i.e., at least 6–10), while reducing morbidity from the procedure.

Although SLN biopsy has been the standard for the axillary staging of patients with invasive breast cancer and a clinically negative axilla, two randomized controlled trials have identified populations for which SLN biopsy could be omitted.

Evidence (omission of SLN biopsy):

1. The SOUND trial (NCT02167490), a multicenter, noninferiority, randomized clinical trial, evaluated omitting SLN biopsy in women with invasive breast cancer. Patients were of any age, had tumors smaller than 2 cm, had negative preoperative axillary ultrasonography, and planned to receive breast-conserving surgery and adjuvant radiation therapy. A total of 1,493 women were randomly assigned to undergo SLN biopsy or no axillary surgery. The median follow-up was 5.7 years.
    - The 5-year distant DFS rate was 97.7% in the SLN biopsy group and 98.0% in the no-surgery group (log-rank P = .67; HR, 0.84; 90% CI, 0.45–1.54; noninferiority P = .02).

- A total of 12 locoregional relapses (1.7%), 13 distant metastases (1.8%), and 21 deaths (3.0%) were observed in the SLN biopsy group, compared with 11 locoregional relapses (1.6%), 14 distant metastases (2.0%), and 18 deaths (2.6%) in the no-surgery group.

2. The multicenter, noninferiority, randomized INSEMA trial (NCT02466737) evaluated omitting SLN biopsy in 5,502 women with clinically node-negative invasive breast cancer. Tumors had to be smaller than 5 cm, and most patients had T1 disease and ER-positive tumors. Patients were scheduled to undergo breast-conserving surgery and whole-breast radiation therapy. Patients were randomly assigned in a 1:4 ratio to undergo no axillary surgery or SLN biopsy. The median follow-up was 6 years.

    - The 5-year invasive DFS rate was 91.9% in the no-surgery group and 91.7% in the SLN biopsy group (HR, 0.91; 95% CI, 0.73–1.14), which was below the prespecified noninferiority margin.
    - Patients in the no-surgery group had a lower incidence of lymphedema, greater arm mobility, and less pain with movement of the arm or shoulder than patients who underwent SLN biopsy.

Breast reconstruction

For patients who opt for a total mastectomy, reconstructive surgery may be performed at the time of the mastectomy (immediate reconstruction) or at some subsequent time (delayed reconstruction). Breast contour can be restored by the following procedures:

- **Mastopexy.**
- **Submuscular insertion of an artificial implant (silicone or saline filled).** If an immediate implant cannot technically be performed, a tissue expander can be inserted beneath the pectoral muscle. Saline is injected into the expander to stretch the tissues for a period of weeks or months until the desired volume is obtained. The tissue expander is then replaced by a permanent implant. For more information on breast implants, see the U.S. Food and Drug Administration.
- **Rectus muscle or other flap.** Muscle flaps require a considerably more complicated and prolonged operative procedure, and blood transfusions may be required.

After breast reconstruction, radiation therapy can be delivered to the chest wall and regional nodes if indicated in either the adjuvant or local recurrent disease setting. Radiation therapy after reconstruction with either a breast prosthesis or a tissue flap may affect cosmesis and symmetry. The incidence of capsular fibrosis, pain, or the need for implant removal may also be increased.

Current clinical trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

Radiation therapy for breast cancer

Radiation therapy is standard after breast-conserving surgery as part of breast-conserving therapy. Radiation therapy is also considered for high-risk postmastectomy patients. The main goal of adjuvant radiation therapy is to eradicate residual disease, reducing local recurrence and increasing breast cancer–specific survival.

Post–breast–conserving surgery

For women who have breast-conserving surgery without radiation therapy, the risk of recurrence in the conserved breast is substantial (>20%) even in women with confirmed axillary lymph

node–negative disease. Although all trials assessing the role of radiation therapy in breast-conserving therapy have shown highly statistically significant reductions in local recurrence rate, no single trial has demonstrated a statistically significant reduction in mortality. However, a large meta-analysis demonstrated a significant reduction in risk of recurrence and breast cancer death. Overall, evidence supports the use of whole-breast radiation therapy after breast-conserving surgery.

Evidence (breast-conserving surgery followed by radiation therapy):

1. A 2011 meta-analysis of 17 clinical trials performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included over 10,000 women with early-stage breast cancer, supported whole-breast radiation therapy after breast-conserving surgery.
    - Whole-breast radiation therapy resulted in a significant reduction in the 10-year risk of recurrence compared with breast-conserving surgery alone (19% for whole-breast radiation therapy vs. 35% for breast-conserving surgery alone; relative risk [RR], 0.52; 95% confidence interval [CI], 0.48–0.56) and a significant reduction in the 15-year risk of breast cancer death (21% for whole-breast radiation therapy vs. 25% for breast-conserving surgery alone; RR, 0.82; 95% CI, 0.75–0.90).

Regarding radiation dosing and schedule, the following has been noted:

- **Whole-breast radiation dose.** Conventional whole-breast radiation therapy is delivered to the whole breast (with or without regional lymph nodes) in 1.8 Gy to 2 Gy daily fractions over 5 to 6.5 weeks to a total dose of 45 Gy to 50 Gy.
- **Radiation boost.** A further radiation boost is commonly given to the tumor bed. Two randomized trials conducted in Europe have shown that boosts of 10 Gy to 16 Gy reduce the risk of local recurrence from 4.6% to 3.6% at 3 years ($P = .044$), and from 7.3% to 4.3% at 5 years ($P < .001$). Results were similar after a median follow-up of 17.2 years. If a boost is used, it can be delivered either by external-beam radiation therapy, generally with electrons, or by using an interstitial radioactive implant. Administering a radiation boost may, however, be associated with unfavorable quality-of-life outcomes.
- **Radiation schedule.** Some studies show that a shorter fractionation schedule of 42.5 Gy over 3 to 4 weeks is a reasonable alternative for some patients with breast cancer.
    - A noninferiority trial of 1,234 randomly assigned patients with node-negative invasive breast cancer analyzed locoregional recurrence rates with conventional whole-breast radiation therapy versus a shorter fractionation schedule. The 10-year locoregional relapse rate among women who received shorter fractionation was not inferior to conventional whole-breast radiation therapy (6.2% for a shorter fractionation schedule vs. 6.7% for whole-breast radiation therapy with absolute difference, 0.5 percentage points; 95% CI, −2.5 to 3.5).
    - Similarly, a combined analysis of the randomized United Kingdom Standardisation of Breast Radiotherapy trials (START), (START-A [ISRCTN59368779]) and START-B [ISRCTN59368779]) revealed no difference in a 10-year locoregional relapse rate. These trials collectively randomly assigned 4,451 women with completely excised invasive (pT1–3a, pN0–1, M0) early-stage breast cancer after breast-conserving surgery to receive conventional whole-breast radiation therapy dosing or shorter fractionation.
    - A meta-analysis that included the three trials mentioned above plus six others confirmed that differences with respect to local recurrence or cosmesis between shorter and conventional fractionation schedules were neither statistically nor clinically significant.

Additional studies are needed to determine whether shorter fractionation is appropriate for women with higher nodal disease burden.

Omission of radiation therapy for favorable, early-stage breast cancer

The omission of radiation therapy after breast-conserving surgery has been tested in older patients with early-stage (T1 and small T2), hormone receptor–positive tumors after primary surgery. Two large trials found that radiation can be safely omitted without survival deficit, but with an increased risk of local recurrence of about 8% at 10 years, assuming that hormonal therapy is used.

1. CALGB 9343 was a phase III randomized trial of radiation omission. A total of 636 women were enrolled; 317 women received tamoxifen plus radiation therapy, and 319 women received tamoxifen alone. Eligible women were aged 70 years or older and had clinical stage I estrogen receptor (ER)-positive breast cancer. Initial eligibility criteria included breast cancers measuring up to 4 cm regardless of ER status, but in August 1996 this was reduced to measuring up to 2 cm (T1) with ER-positive or indeterminate receptor status. Patients were required to have clinically negative axillae.
    - At 10 years, 98% of patients in the tamoxifen-plus-radiation group (95% CI, 96%–99%) were free from local and regional recurrences compared with 90% in the tamoxifen-alone group (95% CI, 85%–93%).
    - There were no significant differences in time-to-mastectomy, time-to-distant metastasis, breast cancer–specific survival, or survival between the two groups. The 10-year overall survival (OS) rate was 67% (95% CI, 62%–72%) in the tamoxifen-plus-radiation group, and 66% (95% CI, 61%–71%) in the tamoxifen-alone group.
2. PRIME-II was a phase III trial of radiation omission. A total of 1,326 women were randomly assigned to receive either whole-breast irradiation (n = 658) or no irradiation (n = 668). Eligible women were aged 65 years or older and had hormone receptor–positive, node-negative, T1 or T2 primary breast cancer (with tumors measuring ≤3 cm in the largest dimension). Patients had previously undergone breast-conserving surgery with clear excision margins and adjuvant endocrine therapy.
    - At a median follow-up of 10 years, the cumulative incidence of local breast cancer recurrence was 9.5% (95% CI, 6.8%–12.3%) in the no-radiation therapy group and 0.9% (95% CI, 0.1%–1.7%) in the radiation therapy group. The 10-year OS rate was almost identical in the two groups, at 80.8% (95% CI, 77.2%–84.3%) in the no-radiation therapy group and 80.7% (95% CI, 76.9%–84.3%) in the radiation therapy group.

Partial breast irradiation

Guidelines that address identifying appropriate candidates for partial breast irradiation have been published.

Evidence (partial breast irradiation):

1. The RAPID trial (NCT00282035) randomly assigned 2,135 women aged 40 years or older with ductal carcinoma *in situ* or node-negative breast cancer treated by breast-conserving surgery to receive either external-beam accelerated partial breast irradiation (APBI) (38.5 Gy in ten fractions delivered twice per day over 5–8 days) or whole-breast radiation therapy (42.5 Gy in 16 fractions delivered once per day over 21 days, or 50 Gy in 25 fractions once per day over 35 days). Sixty-five ipsilateral breast tumor recurrences were observed, 37 in the APBI group, and 28 in the whole-breast irradiation group.
    - In patients treated with APBI, the 5-year cumulative rate of ipsilateral breast tumor recurrence was 2.3% (95% CI, 1.4%–3.2%) and the 8-year cumulative rate was 3.0% (95% CI, 1.9%–4.0%).
    - In patients treated with whole-breast radiation therapy, the 5-year cumulative rate of ipsilateral breast tumor recurrence was 1.7% (range, 0.9%–2.5%) and the 8-year cumulative rate was 2.8% (range, 1.8%–3.9%).
    - The hazard ratio (HR) for APBI versus whole-breast radiation therapy was 1.27 (90% CI, 0.84–1.91).

- Thus, the upper bound of the estimated 90% CI did not exceed the noninferiority margin of 2.02. The APBI arm was associated with less short-term but more long-term toxicity.

2. The NSABP B-39/RTOG 0413 trial (NCT00103181) randomly assigned 4,216 women to whole-breast radiation therapy or APBI. Whole-breast radiation therapy was delivered in 25 daily fractions of 50 Gy over 5 weeks, with or without a supplemental boost to the tumor bed, and APBI was delivered as 34 Gy of brachytherapy or 38.5 Gy of external-bream radiation therapy in 10 fractions, over 5 treatment days within an 8-day period.

    - At a median follow-up of 10.2 years (interquartile range, 7.5–11.5), 90 of 2,089 women (4%) eligible for the primary outcome in the APBI group and 71 of 2,036 women (3%) in the whole-breast radiation therapy group had an ipsilateral breast tumor recurrence (HR, 1.22; 90% CI, 0.94–1.58). The results did not meet the prespecified criterion for equivalence, an HR of 1.50 or less.

    - Toxicity was not substantially different between the arms.

3. The randomized, phase III, single-center APBI-IMRT-Florence trial (NCT02104895) evaluated differences in ipsilateral breast tumor recurrence (IBTR) among patients who received APBI using either intensity-modulated radiation therapy, an advanced radiation technique, (30 Gy in five once-daily fractions) or whole-breast radiation therapy with tangents (50 Gy in 25 fractions with a tumor bed boost). Patients had previously undergone breast-conserving surgery. A total of 520 patients were randomly assigned (whole-breast radiation therapy, n = 260; APBI, n = 260).

    - The 10-year cumulative incidence of IBTR was 2.5% in the whole-breast radiation therapy arm and 3.7% in the APBI arm (HR, 1.56; 95% CI, 0.55–4.37; *P* = .40).

    - The 10-year OS rate was 91.9% in both arms (HR, 0.95; 95% CI, 0.50–1.79; *P* = .86). Breast cancer–specific survival at 10 years was 96.7% in the whole-breast radiation therapy arm and 97.8% in the APBI arm (HR, 0.65; 95% CI, 0.21–1.99; *P* = .45).

    - There were fewer acute and late toxicities in the APBI arm (*P* = .0001 for both comparisons). The APBI arm had improved cosmetic outcomes as evaluated by both physicians and patients (*P* = .0001 for both comparisons).

Regional nodal irradiation

Regional nodal irradiation is routinely given postmastectomy to patients with involved lymph nodes; however, its role in patients who have breast-conserving surgery and whole-breast radiation therapy has been less clear. A randomized trial (NCT00005957) of 1,832 women showed that administering regional nodal irradiation after breast-conserving surgery and whole-breast radiation therapy reduced the risk of recurrence (10-year disease-free survival [DFS] rate, 82.0% vs. 77.0%; HR, 0.76; 95% CI, 0.61–0.94; *P* = .01) but did not affect survival (10-year OS rate, 82.8% vs. 81.8%; HR, 0.91; 95% CI, 0.72–1.13; *P* = .38).

Similar findings were reported from the EORTC trial (NCT00002851). Women with a centrally or medially located primary tumor with or without axillary node involvement, or an externally located tumor with axillary involvement, were randomly assigned to receive whole-breast or thoracic-wall radiation therapy in addition to regional nodal irradiation or not. Breast-conserving surgery was performed for 76.1% of the study population, and the remaining participants underwent mastectomy. No improvement in OS was seen at 10 years among patients who underwent regional nodal irradiation, compared with patients who did not undergo regional nodal radiation (82.3% vs. 80.7%, *P* = .06). Distant DFS was improved among patients who underwent regional nodal irradiation when compared with patients who did not undergo regional nodal irradiation (78% vs. 75%, *P* = .02).

A meta-analysis of individual patient data from all randomized trials of regional lymph node radiation therapy versus no regional lymph node radiation therapy in women with early breast cancer included 16 clinical trials involving 14,324 participants. It found that radiation therapy significantly reduced breast cancer mortality (RR, 0.87; 95% CI, 0.80–0.94; *P* = .0010), with no significant effect on non–breast cancer mortality (RR, 0.97; 0.84–1.11; *P* = .63), leading to significantly reduced all-cause mortality (RR, 0.90; 0.84–0.96; *P* = .0022). Estimated absolute reductions in 15-year breast

cancer mortality were 1.6% for women with zero positive axillary nodes, 2.7% for those with one to three positive axillary nodes, and 4.5% for those with four or more positive axillary nodes.

Postmastectomy

Postoperative chest wall and regional lymph node adjuvant radiation therapy has traditionally been given to selected patients considered at high risk of locoregional failure after mastectomy. Patients at highest risk of local recurrence meet one or more of the following criteria:

- Four or more positive axillary nodes.
- Grossly evident extracapsular nodal extension.
- Lymphovascular space invasion.
- Large primary tumors.
- Very close or positive deep margins of resection of the primary tumor.

In this high-risk group, radiation therapy can decrease locoregional recurrence, even among patients who receive adjuvant chemotherapy.

Patients with one to three involved nodes without any of the high-risk factors may be at a lower risk of local recurrence, and the value of routine use of adjuvant radiation therapy in this setting is an area of controversy.

Evidence (postoperative radiation therapy in patients with one to three involved lymph nodes):

1. The 2005 EBCTCG meta-analysis of 42,000 women in 78 randomized treatment comparisons indicated that radiation therapy is beneficial, regardless of the number of lymph nodes involved.
    - For women with node-positive disease postmastectomy and axillary clearance (removal of axillary lymph nodes and surrounding fat), radiation therapy reduced the 5-year local recurrence risk from 23% to 6% (absolute gain, 17%; 95% CI, 15.2%–18.8%). This translated into a significant reduction ($P = .002$) in breast cancer mortality, 54.7% versus 60.1%, with an absolute gain of 5.4% (95% CI, 2.9%–7.9%).
    - In subgroup analyses, the 5-year local recurrence rate was reduced by 12% (95% CI, 8%–16%) for women with one to three involved lymph nodes and by 14% (95% CI, 10%–18%) for women with four or more involved lymph nodes. In an updated meta-analysis of 1,314 women with axillary dissection and one to three positive nodes, radiation therapy reduced locoregional recurrence (2-sided $P < .00001$), overall recurrence (RR, 0.68; 95% CI, 0.57–0.82; 2-sided $P = .00006$), and breast cancer mortality (RR, 0.80; 95% CI, 0.67–0.95; 2-sided $P = .01$).
    - In contrast, for women at low risk of local recurrence with node-negative disease, the absolute reduction in 5-year local recurrence was only 4% ($P = .002$; 95% CI, 1.8%–6.2%), and there was not a statistically significant reduction in 15-year breast cancer mortality (absolute gain, 1.0%; $P > .1$; 95% CI, -0.8%–2.8%).

Further, an analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) trials showed that even in patients with large (>5 cm) primary tumors and negative axillary lymph nodes, the risk of isolated locoregional recurrence was low enough (7.1%) that routine locoregional radiation therapy was not warranted.

Timing of postoperative radiation therapy

The optimal sequence of adjuvant chemotherapy and radiation therapy after breast-conserving surgery has been studied. Based on studies, delaying radiation therapy for several months after breast-conserving surgery until the completion of adjuvant chemotherapy does not appear to have a negative

impact on overall outcome. Additionally, initiating chemotherapy soon after breast-conserving surgery may be preferable for patients at high risk of distant dissemination.

Evidence (timing of postoperative radiation therapy):

1. In a randomized trial, patients received one of the following regimens:
    - Chemotherapy first (n = 122), consisting of cyclophosphamide, methotrexate, fluorouracil (5-FU), and prednisone plus doxorubicin repeated every 21 days for four cycles, followed by breast radiation.
    - Breast radiation first (n = 122), followed by the same chemotherapy.
2. The following results were observed:
    - With a median follow-up of 5 years, OS was 73% for the radiation-first group and 81% for the chemotherapy-first group (*P* = .11).
    - The 5-year crude rate of first recurrence by site was 5% in the radiation-first group and 14% in the chemotherapy-first group for local recurrence and 32% in the radiation-first group and 20% in the chemotherapy-first group for distant or regional recurrence or both. This difference in the pattern of recurrence was of borderline statistical significance (*P* = .07).
    - Further analyses revealed that differences in recurrence patterns persisted for most subgroups except for those who had either negative tumor margins or one to three positive lymph nodes. For these two subgroups, sequence assignment made little difference in local or distant recurrence rates, although the statistical power of these subgroup analyses was low.
    - Potential explanations for the increase in distant recurrence noted in the radiation-first group are that chemotherapy was delayed for a median of 17 weeks after surgery, and that this group received lower chemotherapy dosages because of increased myelosuppression.
3. Two additional randomized trials, though not specifically designed to address the timing of radiation therapy and adjuvant chemotherapy, do add useful information.
    - In the NSABP-B-15 trial, patients who had undergone breast-conserving surgery received either one course of cyclophosphamide, methotrexate, and 5-FU (CMF) (n = 194) followed by radiation therapy followed by five additional cycles of CMF, or they received four cycles of doxorubicin and cyclophosphamide (n = 199) followed by radiation therapy.
    - No differences in DFS, distant DFS, and OS were observed between these two arms.
    - The International Breast Cancer Study Group trials VI and VII also varied the timing of radiation therapy with CMF adjuvant chemotherapy and reported results similar to NSABP-B-15.

These studies showed that delaying radiation therapy for 2 to 7 months after surgery had no effect on the rate of local recurrence. These findings have been confirmed in a meta-analysis.

In an unplanned analysis of patients treated on a phase III trial evaluating the benefit of adding trastuzumab in HER2-positive breast cancer patients, there was no associated increase in acute adverse events or frequency of cardiac events in patients who received concurrent adjuvant radiation therapy and trastuzumab.[31] Therefore, delivering radiation therapy concomitantly with trastuzumab appears to be safe and avoids additional delay in radiation therapy treatment initiation.

Acute and late toxicities of radiation therapy

Acute toxicities of radiation therapy include radiation dermatitis, breast swelling and/or itching, tightness in the axillary area, and fatigue. If regional nodes are being treated, patients can also experience nausea and a sore throat due to radiation esophagitis. Symptoms typically peak 1 to 2 weeks after radiation therapy, then decrease slowly over the next 4 to 6 weeks.

Late toxicities of radiation therapy are uncommon and can be minimized with radiation delivery techniques and with careful delineation of the target volume. Late effects of radiation include:

- **Radiation pneumonitis.** In a retrospective analysis of 1,624 women treated with conservative surgery and adjuvant breast radiation at a single institution, the overall incidence of symptomatic radiation pneumonitis was 1.0% at a median follow-up of 77 months. The incidence of pneumonitis increased to 3.0% with the use of a supraclavicular radiation field and to 8.8% when concurrent chemotherapy was administered. The incidence was only 1.3% in patients who received sequential chemotherapy.
- **Cardiac events.** Controversy existed as to whether adjuvant radiation therapy to the left chest wall or breast, with or without inclusion of the regional lymphatics, was associated with increased cardiac mortality. In women treated with radiation therapy before 1980, an increased cardiac death rate was noted after 10 to 15 years, compared with women with nonradiated or right-side-only radiated breast cancer.

  This was probably caused by the radiation received by the left myocardium. Modern radiation therapy techniques introduced in the 1990s minimized deep radiation to the underlying myocardium when left-sided chest wall or left-breast radiation was used. Cardiac mortality decreased accordingly.

  An analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) data from 1973 to 1989 that reviewed deaths caused by ischemic heart disease in women who received breast or chest wall radiation showed that since 1980, no increased death rate resulting from ischemic heart disease in women who received left chest wall or breast radiation was found.

  A population-based case-control study evaluated major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2,168 women who underwent radiation therapy for breast cancer. The study found the overall average mean dose to the whole heart was 4.9 Gy (range, 0.03–27.72). The rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy (95% CI, 2.9%–14.5%; $P < .001$), with no apparent threshold.

- **Arm lymphedema.** Lymphedema remains a major quality-of-life concern for breast cancer patients. Single-modality treatment of the axilla (surgery or radiation) is associated with a low incidence of arm edema. In patients who receive axillary dissection, adjuvant radiation therapy increases the risk of arm edema. Edema occurs in 2% to 10% of patients who receive axillary dissection alone compared with 13% to 18% of patients who receive axillary dissection and adjuvant radiation therapy.
- **Brachial plexopathy.** Radiation injury to the brachial plexus after adjuvant nodal radiation therapy is a rare clinical entity for breast cancer patients. In a single-institution study using current radiation techniques, 449 breast cancer patients treated with postoperative radiation therapy to the breast and regional lymphatics were monitored for 5.5 years to assess the rate of brachial plexus injury. The diagnosis of such injury was made clinically with computed tomography to distinguish radiation injury from tumor recurrence. When 54 Gy in 30 fractions was delivered to the regional nodes, the incidence of symptomatic brachial plexus injury was 1.0%, compared with 5.9% when increased fraction sizes (45 Gy in 15 fractions) were used.
- **Contralateral breast cancer.** One report suggested an increase in contralateral breast cancer for women younger than 45 years who received chest wall radiation therapy after mastectomy. No increased risk of contralateral breast cancer occurred in women aged 45 years and older who received radiation therapy. Techniques to minimize the radiation dose to the contralateral breast are used to keep the absolute risk as low as possible.

- **Risk of second malignancy.** The rate of second malignancy after adjuvant radiation therapy is very low. Sarcomas in the treated field are rare, with a long-term risk of 0.2% at 10 years. In nonsmokers, the risk of lung cancer as a result of radiation exposure during treatment is minimal when current dosimetry techniques are used. Smokers, however, may have a small increased risk of lung cancer in the ipsilateral lung.

Current clinical trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

Systemic therapy for stages I, II, and III breast cancer

The first decision about the use of systemic therapy in patients with stages I, II and III breast cancer is whether it should be given before or after surgery. This section outlines factors to consider when making this decision. Information about the treatment of locally advanced or inflammatory breast cancer is also included in this section.

Preoperative chemotherapy, also known as primary or neoadjuvant chemotherapy, has traditionally been given to patients with locally advanced breast cancer to reduce tumor volume and allow for definitive surgery. Treatment with preoperative chemotherapy can also allow for breast conservation therapy in patients who are not candidates for breast conservation at initial presentation. Preoperative chemotherapy may also reduce the need for an axillary lymph node dissection (ALND) in patients presenting with node-positive disease.

Much of the evidence presented in the following sections on preoperative chemotherapy is discussed in an American Society of Clinical Oncology guideline that describes the selection of options for the management of these patients.

A 2005 meta-analysis of multiple randomized clinical trials demonstrated that preoperative chemotherapy is associated with identical disease-free survival (DFS) and overall survival (OS) as the same therapy in the adjuvant setting.

In 2019, the Early Breast Cancer Trialists' Collaborative Group performed a meta-analysis using individual patient data from 4,756 women who participated in 10 trials that compared neoadjuvant chemotherapy with the same regimen given in the adjuvant setting.

Compared with adjuvant therapy, neoadjuvant therapy was associated with an increased frequency of breast conservation (65% vs. 49%). There were no differences between neoadjuvant chemotherapy and adjuvant therapy in distant recurrence, breast cancer mortality, or death from any cause. However, neoadjuvant therapy was associated with higher 15-year local recurrence rates (21.4% vs. 15.9%; relative risk [RR], 1.37; 95% confidence interval [CI], 1.17−1.61; P = .001).

Pathological complete response (pCR) has been used as a surrogate end point for long-term outcomes, such as DFS, event-free survival (EFS), and OS, in preoperative clinical trials in breast cancer. A pooled analysis (CTNeoBC) of 11 preoperative randomized trials (n = 11,955) determined that pCR, defined as no residual invasive cancer in the breast and axillary nodes with presence or absence of *in situ* cancer (ypT0/is ypN0 or ypT0 ypN0), was associated with improved outcomes compared with eradication of invasive tumor from the breast alone (ypT0/is).[4] pCR could not be validated in this study as a surrogate end point for improved EFS and OS. Because of a strong association between pCR and substantially improved outcomes in individual patients with more aggressive subtypes of breast cancer, the U.S. Food and Drug Administration (FDA) has supported use of pCR as an end point in preoperative clinical trials for patients with high-risk, early-stage breast cancer.

Unfortunately, categorizing patients as having pCR or residual disease offers no distinction among patients with varied amounts of residual disease. The residual cancer burden (RCB) method was designed to address this and other prognostic deficits. The RCB method provides a standard to

evaluate and quantify the extent of residual disease in breast and axillary lymph nodes following neoadjuvant chemotherapy. It is reported as a continuous score, with pCR being scored as RCB-0. There are four RCB classes ranging from RCB-0 to RCB-3. Determining RCB after neoadjuvant treatment has been validated as a prognostic predictor in early breast cancer.

A pooled, multinational, multi-institutional analysis was performed, using participant-level RCB results and clinicopathological data. Data from 5,161 patients were analyzed to assess the association between the continuous RCB score and the primary study outcome, EFS. With a median follow-up of 56 months, the RCB score was prognostic within each breast cancer subtype, with a higher RCB score significantly associated with worse EFS. RCB score was prognostic for EFS in multivariable models adjusted for age, grade, T (tumor) category, and nodal status at baseline. The adjusted hazard ratio (HR) associated with a one-unit increase in RCB ranged from 1.52 in the HER2-negative hormone receptor–positive group to 2.09 in the HER2-positive hormone receptor–negative group ($P < .0001$ for all subtypes).

Neoadjuvant therapy is particularly favored in patients with triple-negative or HER2-positive disease, when pathological response is used as a guide in choosing the optimal adjuvant therapy after surgery. For more information, see the sections on Stages I, II, and III Triple-Negative Breast Cancer and Stages I, II, and III HER2-Positive Breast Cancer.

Omission of postoperative radiation therapy to the regional nodes in patients who initially present as node positive and become node negative after neoadjuvant therapy is currently being evaluated.

Reference

PDQ® Adult Treatment Editorial Board (2025, April 25). *PDQ breast cancer treatment*. National Cancer Institute. https://www.cancer.gov/types/breast/hp/breast-treatment-pdq