Overview of Radiation Oncology Evaluation and Management of Breast Tumors

5

Todd C. Adams, Nicholas Serrano, Christopher Chipko, and Douglas W. Arthur

Radiation therapy is indicated as part of the standard of care treatment for the majority of patients with breast cancer. Large clinical trials evaluating the efficacy of radiation treatment for breast cancer date back more than a half century. This chapter discusses the indications for adjuvant radiation therapy for ductal carcinoma in situ and invasive breast cancer. It explores the data supporting the indications for radiation therapy and the benefit of radiation therapy in various clinical settings. Also discussed are the role of regional nodal irradiation, the indications for shorter radiation treatment schedules, and the benefit of a radiation boost. This chapter further addresses the role of partial breast irradiation, and lastly, it discusses the clinical scenarios where omission of radiation may be considered. The role of radiation in treating breast angiosarcomas and malignant phyllodes tumors is not addressed here because these topics are more appropriately discussed in the context of the management of sarcomas.

Ductal Carcinoma In Situ (DCIS)

Local Management Options

Breast-conserving surgery alone, breast-conserving surgery followed by partial-breast irradiation, breast-conserving surgery followed by whole-breast radiotherapy, and mastectomy

T.C. Adams, MD (✉) • N. Serrano, MD • C. Chipko, MD • D.W. Arthur, MD
Department of Radiation Oncology, Virginia Commonwealth University Health (VCU HEALTH), Richmond, VA, USA
e-mail: todd.adams@vcuhealth.org; serranona@vcu.edu; chipkocr@vcu.edu; douglas.arthur@vcuhealth.org

M.O. Idowu et al. (eds.), *Diagnosis and Management of Breast Tumors*,
DOI 10.1007/978-3-319-57726-5_5

Ideal Candidate for Breast-Conserving Treatment

The ideal candidate for breast-conserving treatment is a patient with a unifocal, less than 5 cm breast tumor resected with negative margins at least 2 mm margins for DCIS. The tumor size should be relatively small in comparison to the breast size such that a good postsurgical cosmetic outcome can be achieved. The ideal candidate would be nonpregnant and absent of a history of scleroderma or lupus skin involvement.

Indications for Radiation

Local management decisions for DCIS are influenced by patient preference, patient age, tumor size, tumor grade, and the ability of the resection to achieve both a negative surgical margin and acceptable cosmetic result. Pure DCIS is an in-breast control issue as it lacks the ability to metastasize and therefore has no bearing on overall survival if properly managed. The addition of adjuvant radiation improves local control for all subsets of DCIS patients treated with breast-conserving surgery with no impact on overall survival. The decision to add postoperative radiotherapy is principally a relative risk reduction of in-breast failure (recurrence in the treated breast). Therefore, as the age of the presenting patient becomes younger and the tumor features become more threatening, the risk of in-breast failure following lumpectomy increases and the recommendation for postoperative radiotherapy becomes stronger. General guidelines governing recommendations are as follows: Omission of radiation should be considered as an appropriate option for those women aged 60 and older who receive endocrine therapy; have a small (<2 cm), low- or intermediate-grade, estrogen receptor-positive tumor resected with wide (>2 mm) surgical margins; and have a sufficiently small in-breast recurrence rate without adjuvant radiotherapy, assuming the patient has been informed and accepts the relatively small increase in disease recurrence. For those women presenting with more significant features (who have estrogen-negative disease, who have estrogen-positive disease but are not undergoing endocrine therapy, who are less than 60 years old and have tumors larger than 2 cm, grade 3 tumors, and/or tumors resected with <2 mm margins), the risk of in-breast failure is sufficiently higher that postoperative radiotherapy is considered the standard of care and should be strongly considered. Postmastectomy radiation for DCIS is generally not indicated.

Benefit of Radiation

Adjuvant radiation significantly improves local control but does not affect breast cancer-specific survival or overall survival.

Absolute Radiation Contraindications

Radiation therapy during pregnancy

Relative Contraindications

Active scleroderma or lupus involving the skin, focally positive surgical margin, close surgical margin (1 mm or less), known BRCA1/BRCA2 mutation, and previous radiation therapy to the breast or chest wall

Radiation Technique

Radiation may be given to the *whole breast with standard fractionation* (50 Gy in 25 fractions) or *hypofractionation* (42.56 Gy in 16 fractions). A boost is typically recommended, but omission can be considered for patients aged 60 or older with low volume disease resected with acceptable surgical margins. In appropriately selected patients, radiation may be given to a partial-breast target with *accelerated partial-breast irradiation* (APBI). Patient selection guidelines for APBI use with DCIS are available from several societies [1–3]. APBI can be delivered with *brachytherapy*, 34 Gy in ten fractions given twice daily, or *highly conformal external beam irradiation*, 38.5 Gy in ten fractions given twice daily.

Factors for Consideration

Patient age, patient life expectancy, comorbidities which may increase the risk of complications, tumor size, margin width, tumor grade, tumor histology (i.e., comedonecrosis), hormone receptor status, cosmetic result, and patient expectations

Selected Studies

Mastectomy vs. Breast-Conserving Therapy

There are no DCIS randomized trials comparing mastectomy and breast-conserving therapy (local resection plus radiation). The equivalency of mastectomy and breast-conserving therapy in DCIS can be extrapolated from the rich invasive breast cancer literature comparing these two modalities. Postmastectomy radiation for DCIS is generally not indicated. Breast-conserving surgery followed by adjuvant radiation is a standard-of-care option for the treatment for DCIS. Data supporting the recommendation for postoperative radiation therapy comes from four randomized trials. In sum, these trials showed that adjuvant whole-breast irradiation reduced ipsilateral breast tumor recurrence by approximately 50% compared to observation; overall survival was not improved with radiation.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial randomized 818 patients with DCIS to lumpectomy plus adjuvant radiation or lumpectomy alone [4, 5]. Patients were required to have negative surgical margins, and radiation was delivered to the whole breast to a dose of 50 Gy in 25 fractions without a boost. At a 15-year follow-up, radiation significantly reduced the rate of

ipsilateral breast tumor recurrence from 35.0% in the lumpectomy alone group to 19.8% in the lumpectomy plus adjuvant radiation group (HR 0.48; $P < 0.001$). The decrease in local recurrence was for both invasive and noninvasive recurrences.

The European Organization for Research and Treatment of Cancer (EORTC) produced similar results in their EORTC 10853 trial where they randomized 1010 patients with DCIS to lumpectomy or lumpectomy plus radiation [6]. As in NSABP-B17, patients were required to have clear surgical margins and a radiation dose of 50 Gy in 25 fractions was delivered to the whole breast. While a boost was not recommended, 5% of patients received a tumor bed boost. At 15 years, there was a significant reduction in local recurrences with the addition of radiation therapy, from 31% with lumpectomy alone to 18% with lumpectomy plus radiation (HR 0.52; $P < 0.001$). Subgroup analysis showed there was a benefit of radiation in all subgroups.

The SweDCIS Trial randomized 1067 patients with DCIS to lumpectomy or lumpectomy plus radiation [7]. In this study, patients underwent sector resection which required 1 cm gross surgical margins; microscopically clear margins were not required. Although most patients received conventional radiation of 50 Gy in 25 fractions to the whole breast, a split course of 54 Gy in 28 fractions with a mid-treatment 2-week break was allowed. No boost was allowed. At 20-year follow-up, the ipsilateral breast event cumulative risk was 20.0% in the radiation arm and 32.0% in the lumpectomy alone arm ($P < 0.001$). Subgroup analysis showed that for patients with tumors 14 mm or smaller with negative surgical margins, there was no statistical difference in breast events between lumpectomy plus radiation and lumpectomy alone.

The UK Coordinating Committee on Cancer Research collaborated with Australia and New Zealand to conduct the UK/ANZ DCIS trial which incorporated a 2×2 factorial design to evaluate the benefit of the adjuvant radiation, tamoxifen, or both to breast-conserving surgery [8]. After undergoing lumpectomy with negative margins, patients were randomized to observation, radiation alone, tamoxifen alone, or radiation plus tamoxifen. Randomization was independently performed for radiation and tamoxifen, or the surgeon selected one treatment modality with randomization to the other modality. Radiation was given to the whole breast to a dose of 50 Gy in 25 fractions without a boost. Tamoxifen was given 20 mg daily. After 12.7-year median follow-up of 1071 patients, post-lumpectomy radiation reduced all ipsilateral breast events from 19.4% in patients treated without radiation to 7.1% in patients treated with radiation (HR 0.32; $P < 0.0001$). Radiation reduced ipsilateral invasive disease and ipsilateral DCIS but had no effect on contralateral breast events. The benefit of radiation was irrespective of tamoxifen use. Tamoxifen reduced the incidence of recurrent ipsilateral DCIS and contralateral breast cancer but did not have a significant effect on ipsilateral invasive disease.

At least two meta-analyses have established the role of adjuvant radiation in the treatment of DCIS. In 2010, an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of 3729 DCIS patients treated with breast-conserving surgery showed that adjuvant radiation compared to observation provided a significant reduction in 10-year ipsilateral breast events from 28.1% without radiation to 12.9% with radiation ($p < 0.00001$) [9]. The benefit was significant regardless of age of the patient, extent of breast-conserving surgery, tamoxifen use, negative versus positive margins, unifocal versus multifocal disease, nuclear grade, presence of comedonecrosis, tumor architecture, or tumor size. The proportional benefit was

greater in women aged 50 or older compared to women younger than age 50, but otherwise did not differ with any other evaluable factors. Even for women with small, low-grade tumors resected to negative margins, adjuvant radiation reduced the 10-year risk of ipsilateral breast tumor recurrence from 30.1 to 12.1%.

A Cochrane Database review of the four randomized trials mentioned above confirmed a statistically significant benefit of the addition of adjuvant radiation therapy on ipsilateral recurrent DCIS (HR 0.61; $P = 0.03$), ipsilateral recurrent invasive cancer (HR 0.50; $P = 0.001$), and all ipsilateral breast events (HR 0.49; $P < 0.00001$) [10]. On multivariate analysis, there were no subgroups which did not benefit from the addition of radiation, regardless of completeness of excision, patient age, size of the primary lesion, or the presence or absence of comedonecrosis.

Omission of Adjuvant Radiation in DCIS

Multiple studies have examined the safety of omission of radiation in subsets of DCIS patients. Collectively, these studies show that adjuvant radiation significantly reduces the risk of in-breast failure for all subsets of patients. However, for patients aged 60 and older who receive endocrine therapy and have a small (<2 cm), low- or intermediate-grade, estrogen receptor-positive tumor resected with wide (>2 mm) surgical margins, the risk of in-breast recurrence may be sufficiently low that adjuvant radiation may be avoided if the patient accepts the increased risk of recurrence.

The Van Nuys Prognostic Index uses tumor size, margin width, and pathologic classification as predictors of local recurrence of DCIS to create a score which predicts the risk of local recurrence and the benefit of adjuvant radiation [11, 12]. The scores are used to make treatment recommendations regarding surgery and radiation. The predictors of local recurrence and index scores are based on regression analysis of nonrandomized patient data contained in a prospective database from two institutions.

A single arm prospective trial by Harvard/Dana-Farber Institute evaluated 158 patients with predominantly low- or intermediate-grade DCIS mammographically measuring ≤2.5 cm with surgical margins ≥1 cm [13]. Patients were treated with wide local excision alone without adjuvant radiation or tamoxifen. The 10-year cumulative local recurrence rate was 15.6%. Sixty-nine percent of local recurrences were DCIS and 31% were invasive. The annual rate of local recurrence was 1.9% per patient year.

The Radiation Therapy Oncology Group (RTOG) 9804 study was a randomized trial for patients with good-risk DCIS which compared postoperative radiation therapy with observation alone [14]. Patients had low- or intermediate-grade DCIS measuring less than 2.5 cm resected with margins ≥3 mm. The expected enrollment on the trial was 1790 patients, but the trial closed early due to poor accrual after 636 patients. Tamoxifen, which was optional, was used by 62% of patients. The median pathologic tumor size was 0.5 cm with the pathological margin being between 3–9 mm in 36% of patients and 10 mm or more in 16% of patients. Almost half (48%) of patients underwent re-excision. The 7-year local failure rate was 0.9% in the radiation arm versus 6.7% in the observation arm (HR 0.11; $P < 0.001$). There was no difference in grade 3 or 4 toxicities between the two treatment arms.

Similarly, the Eastern Cooperative Oncology Group (ECOG) E-5194 trial prospectively evaluated two cohorts of low-risk DCIS patients treated with wide local

excision alone [15]. Cohort 1 included patients with low- or intermediate-grade DCIS measuring ≤2.5 cm; cohort 2 included patients with high-grade DCIS measuring ≤1 cm. A minimum 3 mm margin was required. At 12-year follow-up, the ipsilateral breast event rate was 14.4% for cohort 1 and 24.6% for cohort 2. Approximately half (52%) of recurrences were invasive. Although tumor size up to 2.5 cm and margin width as close as 3 mm were allowed, the median tumor size was 5 mm and the median margin width was 1 cm. Even in this favorable-risk population, recurrence rates were significant without radiation.

Radiation Boost and Hypofractionation in DCIS

There are no randomized trials looking specifically at the role of a radiation boost in DCIS patients treated with radiation. The recommendation for a radiation boost is based on extrapolation from randomized trials of patients with low-risk early-stage invasive breast cancer. Similarly, the recommendation for hypofractionation for DCIS patients aged 50 or older is based on prospective randomized trials of patients with early-stage invasive disease.

Invasive Breast Cancer: The Role of Adjuvant Radiation in Breast-Conserving Therapy

Local Management Options

Breast-conserving surgery alone, breast-conserving surgery followed by partial-breast irradiation, and breast-conserving surgery followed by whole-breast radiotherapy (Figs. 5.1 and 5.2).

Ideal Candidate for Breast-Conserving Treatment

The ideal candidate for breast-conserving treatment is a patient with a unifocal, less than 5 cm breast tumor resected with negative margins for invasive disease. The tumor size should be relatively small in comparison to the breast size such that a good postsurgical cosmetic outcome can be achieved. The ideal candidate would be nonpregnant and absent a history of scleroderma or lupus skin involvement.

Indications for Radiation

Adjuvant radiation following breast-conserving surgery for invasive breast cancer improves local control, breast cancer-specific survival, and overall survival. Adjuvant radiation is indicated for patients under the age of 70 who undergo lumpectomy and for patients aged 70 or older who wish to maximize local control. Adjuvant radiation provides a local control benefit for all subgroups of patients, including those aged 70 or older. The absolute local control benefit, however, is less for patients aged 70 or older than for younger patients. Omission of adjuvant radiation is an appropriate option in patients aged 70 or older who will receive 5 years of endocrine therapy and who have small (T1), low- or intermediate-grade, estrogen receptor-positive tumors resected with good margins assuming the patient has been informed and accepts the relatively small increase in disease recurrence.

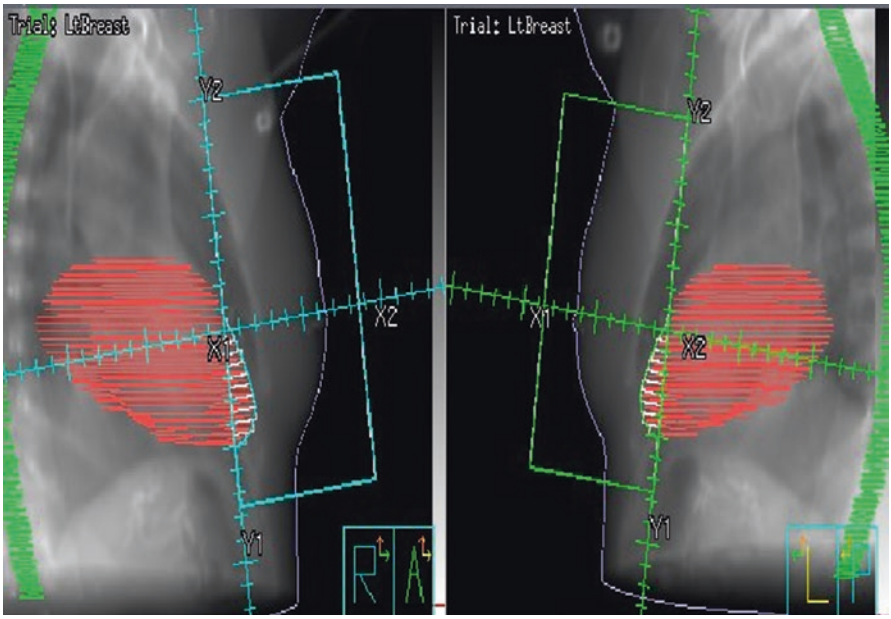

Fig. 5.1 Beam's eye view of tangential whole-breast radiation treatment fields

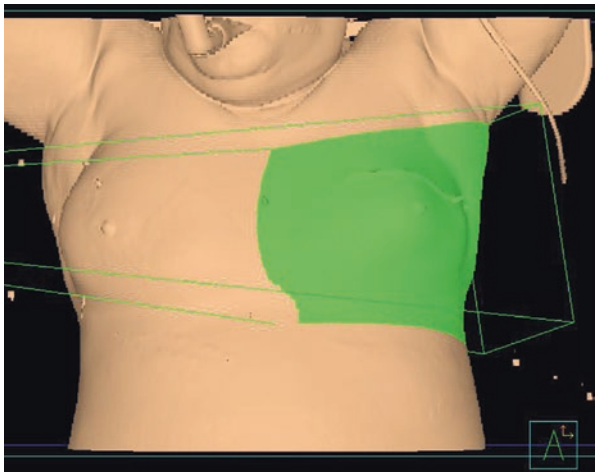

Fig. 5.2 Skin rendering view of a medial tangential whole-breast radiation treatment field

Benefit of Radiation

Adjuvant radiation following breast-conserving surgery for invasive breast cancer improves local control, breast cancer-specific survival, and overall survival.

Absolute Contraindications

Radiation therapy during pregnancy

Relative Contraindications

Active scleroderma or lupus involving the skin, positive surgical margin, known BRCA1/BRCA2 mutation, and previous radiation therapy to the breast

Radiation Technique

Radiation may be given to the whole breast with standard fractionation (50 Gy in 25 fractions) or hypofractionation (42.56 Gy in 16 fractions). A boost is typically recommended, but omission can be considered for patients aged 60 or older with low volume disease resected with acceptable surgical margins. In appropriately selected patients, radiation may be given to the partial-breast target with accelerated partial-breast irradiation (APBI). Patient selection guidelines for APBI use for invasive disease are available from several societies [1–3]. APBI can be delivered with brachytherapy, 34 Gy in ten fractions given twice daily, or highly conformal external beam irradiation, 38.5 Gy in ten fractions given twice daily.

The addition of regional nodal irradiation is recommended for patients with one or more pathologically positive lymph nodes evaluated at surgery or prior to neoadjuvant chemotherapy. Regional nodal irradiation includes the undissected axilla, supraclavicular-axillary apical nodes, and internal mammary nodes.

Factors for Consideration

Patient age, patient life expectancy, comorbidities which may increase the risk of complications, tumor size, margin width, lymphovascular space invasion, number of lymph nodes involved, volume of lymph node involvement, extranodal extension, number of lymph nodes removed, tumor grade, tumor histology, hormone receptor status, HER2/neu status, response to neoadjuvant chemotherapy, cosmetic result, and patient expectations

Selected Studies

Mastectomy vs. Breast-Conserving Therapy for Invasive Breast Cancer

Randomized trials have established that breast-conserving surgery followed by radiation therapy is equivalent to mastectomy for appropriately selected patients with early-stage breast cancer. In all of these trials, segmental mastectomy combined with breast irradiation resulted in survival and local control rates similar to those achieved by modified radical or radical mastectomy.

In 1973 Veronesi et al. began a prospective trial in Milan comparing radical mastectomy to breast-conserving surgery followed by radiation [16]. The study enrolled 701 patients with no palpable axillary lymph nodes and tumors up to 2 cm in diameter. Patients were randomly assigned to receive Halsted radical mastectomy, or quadrantectomy, axillary dissection, and radiation. A radiation dose of 50 Gy given over 5 weeks was delivered to the breast followed by a boost dose of 10 Gy. Patients found to have positive axillary lymph nodes at surgery received 12 cycles of adjuvant cyclophosphamide, methotrexate, and fluorouracil. The 20-year mortality rate from all causes was 41.2% in the radical-mastectomy arm and 41.7% in the breast-conserving surgery plus radiation arm ($P = 1.0$). Mortality from breast cancer was

not significantly different, at 24.3 and 26.1%, respectively ($P = 0.8$). The cumulative incidence of local failure was 2.3% in the mastectomy group and 8.8% in the breast-conserving surgery and radiation group ($P < 0.001$). There was no difference between the groups in the incidence of contralateral breast cancer, distant metastases, or second primary cancers.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the NSABP B-06 trial in the United States in 1976 which enrolled 1843 women with clinical stage I or II breast cancer [17]. Patients were randomly assigned to treatment with total mastectomy, lumpectomy, or lumpectomy with radiation. The prescribed radiation dose was 50 Gy to the breast without a lumpectomy cavity boost. At 20-year follow-up, there was no significant difference in overall survival, disease-free survival, or distant disease-free survival among any of the groups. However, the addition of radiation to lumpectomy significantly decreased the local recurrence rate by half compared to lumpectomy alone with the cumulative ipsilateral breast recurrence being 14.3% in the lumpectomy and radiation group and 39.2% in the lumpectomy alone group ($P < 0.001$).

EORTC 10801 was a randomized trial which compared mastectomy to breast-conserving therapy in 868 women with stage I and II breast cancer [18]. The European Organization for Research and Treatment of Cancer (EORTC) conducted the trial in the United Kingdom, the Netherlands, Belgium, and South Africa and initiated enrollment in 1980. Patients were randomized to modified radical mastectomy or breast-conserving therapy. Breast-conserving therapy consisted of lumpectomy with a 1 cm margin, axillary dissection, and whole-breast irradiation prescribed to 50 Gy with a 25 Gy lumpectomy site boost. At 20-year follow-up, the mortality rate was 55% in the modified radical mastectomy group and 61% in the breast-conserving therapy group, with no significant difference in time to death (HR 1.11; $p = 0.23$). There was also no significant difference in time to distant metastases (HR 1.13; $P = 0.23$) with a distant metastasis rate of 42% in the modified radical mastectomy group and 46% in the breast-conserving therapy group. Time to distant metastases and overall survival were stratified by age less than 50 versus age greater than or equal to 50, and there was no difference between treatment groups. The 15-year overall survival rate was 53.6% in the mastectomy group and 51.6% in the breast-conserving therapy group.

The Institut Gustave Roussy conducted a prospective trial in which 179 patients under age 70 with T1 N0-N1 M0 invasive breast cancer were randomized to modified radical mastectomy or wide lumpectomy, axillary surgery, and adjuvant radiation [19, 20]. Eligible patients had tumors macroscopically measuring 2 cm or less on frozen section at the time of surgery. Lymph node-negative patients received a whole-breast irradiation dose of 45 Gy given in 18 fractions with a 15 Gy tumor bed boost. Patients with positive lymph nodes received whole-breast irradiation and were randomized to radiation treatment of the regional lymph nodes. The 15-year rates of local recurrence, locoregional recurrence, contralateral breast cancer, distant metastases, and overall survival were not statistically different between surgical treatment arms and radiation treatment arms. The 15-year cumulative local

recurrence rate was 13% in the lumpectomy and radiation group and 18% in the mastectomy group ($P = 0.48$). The 15-year rate of any first event was 45% with lumpectomy and radiation and 56% with mastectomy ($P = 0.23$) with 15-year overall death rates of 27 and 35%, respectively ($P = 0.19$).

Radiation vs. Hormonal Therapy

There have been at least nine clinical trials evaluating endocrine therapy as a substitute for radiation. All trials have shown that radiation therapy alone provides improved local control compared to endocrine therapy alone.

Radiation vs. Observation

There have been a number of randomized trials investigating the local control benefit of the addition of postoperative radiation to breast-conserving surgery. In these studies, the addition of postoperative radiation reduced the risk of local recurrence by 50% or more compared to breast-conserving surgery alone. These studies support the role of adjuvant radiation as part of standard-of-care treatment for younger women who select breast-conserving treatment.

Beginning in 1981, the Uppsala-Orebro Breast Cancer Study conducted a randomized trial of breast-conserving surgery with or without radiation in 381 Swedish women with stage I breast cancer [21]. Patients were treated with sector resection and axillary dissection and then randomized adjuvant breast irradiation to 54 Gy or observation. At 5 years, the local recurrence rate was 2.3% in the group that received adjuvant radiation versus 18.4% in the group in which radiation was omitted. Overall survival, regional recurrence-free survival, and distant recurrence-free survival were not different between groups.

As discussed above, NSABP B-06 compared total mastectomy, lumpectomy alone, and lumpectomy plus radiation in 1851 women with clinical stage I and II breast cancer. In 1137 women with negative surgical margins, the 20-year cumulative incidence of ipsilateral breast tumor recurrence was 39.2% in the lumpectomy alone group compared to 14.3% in the lumpectomy plus radiation group ($p < 0.0001$) [17]. For women with negative lymph nodes, the 20-year ipsilateral breast tumor recurrence rates were 36.2% with lumpectomy alone and 17.0% with lumpectomy plus radiation; for women with positive lymph nodes, the ipsilateral breast tumor recurrence rates were 44.2% without radiation versus 8.8% with radiation. Disease-free survival, distant disease-free survival, and overall survival did not differ between any of the groups. Breast cancer-specific mortality was decreased in patients treated with lumpectomy plus radiation compared to lumpectomy alone (HR 0.82, $P = 0.04$). This marginally significant decrease in breast cancer mortality may have been partially offset by deaths from other causes (HR 1.23; $P = 0.23$).

Because of the uncertainty regarding the need for radiation in women with favorable risk factors, the NSABP initiated NSAPB B-21 which enrolled 1009 women with tumors clinically or pathologically <1 cm in size who were treated with lumpectomy and axillary dissection [22]. Patients were required to have negative lymph nodes and negative margins on pathology review. Patients were randomized to tamoxifen only, radiation and placebo, or radiation and tamoxifen. At 8 years, the cumulative incidence of local relapse was 16.5% in the tamoxifen alone group, 9.3% in the radiation and placebo group, and 2.8% in the radiation and tamoxifen group. The respective hazard ratios for ipsilateral breast tumor recurrence were HR 0.51 ($P = 0.008$) for radiation plus placebo versus tamoxifen alone, HR 0.37 ($P = 0.01$) for radiation plus tamoxifen versus radiation plus placebo, and HR 0.19 ($P < 0.0001$) for radiation plus tamoxifen versus tamoxifen alone. Tamoxifen decreased the occurrence of contralateral breast cancer compared to radiation plus placebo (HR 0.45; $P = 0.039$). There was no difference in overall survival or distant metastases between groups.

Veronesi et al. at the Milan National Cancer Institute also investigated the efficacy of breast-conserving surgery without radiation in a study where 579 women under the age of 70 with breast cancer less than 2.5 cm in size were randomized to quadrantectomy, axillary dissection, and radiation, or the same surgery without radiation [23]. The 10-year crude ipsilateral breast tumor recurrence rate was 23.5% for patients treated without radiation and 5.8% for patients who received radiation. The cumulative hazard rate for ipsilateral recurrence was significant ($P < 0.001$). Overall survival was not statistically different between the treatment arms; however, on subset analysis, patients with node-positive disease had improved survival with radiation ($P = 0.038$) with a crude mortality rate of 34.1% in the radiation omission group versus 19.1% for group who received radiation. Subset analysis also showed that the group which radiation provided the greatest decrease in ipsilateral recurrence was patients aged 45 and younger. In older age groups, the difference in ipsilateral recurrence tended decrease until no difference was seen after age 65.

Meta-analyses of Radiation in Breast-Conserving Therapy

Two comprehensive meta-analyses of the benefit of postoperative radiation added to breast-conserving surgery suggest that adjuvant radiation significantly decreases local recurrence, breast cancer mortality, and overall mortality.

In 2005, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis of individual patient data from 7311 patients with invasive breast cancer treated on clinical trials comparing breast-conserving surgery with radiation to breast-conserving surgery without radiation [24]. The meta-analysis showed that radiation significantly improved 15-year local recurrence and 15-year breast cancer-specific survival compared to no radiation and radiation significantly improved 15-year overall mortality by 5.3% (35.2 versus 40.5%). The analysis also showed three-fourths of breast recurrences occurred in the first 5 years following treatment.

The Early Breast Cancer Trialists' Collaborative Group updated the meta-analysis in 2011 to include individual data on 10,801 patients treated on 17 randomized trials comparing adjuvant radiation versus observation after breast-conserving surgery [25]. The update showed that compared to observation, adjuvant radiation significantly decreased the 10-year risk of any first recurrence from 35.0 to 19.3% (RR 0.52). Radiation also significantly reduced the 10-year risk of breast cancer mortality from 25.2 to 21.4% (RR 0.82) and significantly decreased the 15-year risk of overall mortality from 37.6 versus 34.6% (RR 0.92). For women with node-positive disease, the benefits of radiation were even greater with radiation reducing the 10-year risk of any first recurrence from 63.7 to 42.5% and improving the 15-year risk of breast cancer mortality from 51.3 to 42.8%.

Omission of Radiation in Older Patients

Lumpectomy followed by radiation is a standard of care option for the majority of women with early-stage invasive breast cancer. As observed in randomized trials, lumpectomy without radiation results in increased local relapse. However, trials examining the omission of radiation found that in elderly women, local relapse rates were lower and radiation provided a lower absolute local control benefit without improving overall survival. The question of whether radiation can be safely eliminated following breast-conserving therapy for elderly patients has been studied with retrospective and prospective studies which are reviewed below. In sum, these studies show adjuvant radiation improves local control for older women with favorable-risk disease without improving overall survival. For patients aged 70 or older who will receive 5 years of endocrine therapy and who have small (T1), low- or intermediate-grade, estrogen receptor-positive tumors resected with good margins, the risk of disease recurrence may be acceptably low such that adjuvant radiation may be omitted if the patient accepts the increased risk of recurrence associated with radiation omission.

CALGB (Cancer and Leukemia Group B) 9343 was a trial which evaluated the effect of radiation omission in older patients with favorable-risk breast cancer [26]. The trial evaluated 636 women aged 70 or older with clinically node-negative, estrogen receptor-positive breast cancer measuring 2 cm or less who were treated with lumpectomy with negative pathological margins. Axillary dissection was permissible but not required. Patients were randomized to receive tamoxifen 20 mg for 5 years plus whole-breast irradiation with a boost or tamoxifen alone for 5 years. With a median follow-up of 12.6 years, the 10-year rate of locoregional recurrence was 10% in the tamoxifen alone arm versus 2% in the tamoxifen plus radiation arm (HR 0.18; $p < 0.001$). The published study did not analyze pathologic tumor size or margin width. Overall survival at 10 years was 67% in the tamoxifen plus radiation group and 66% in the tamoxifen alone group. Overall survival, breast cancer-specific survival, time to mastectomy, and time to distant metastasis were not statistically different between groups.

Fyles et al. performed a trial in Canada which enrolled 769 women aged 50 or older with node-negative invasive breast cancer and tumor size of 5 cm or less on

pathologic review [27]. Patients were treated with breast-conserving surgery with negative pathologic margins and then randomized to whole-breast irradiation plus tamoxifen 20 mg for 5 years or tamoxifen alone. Most patients were aged 60 or older, most tumors were less than 2 cm, and more than 80% of tumors were hormone receptor positive. The 5-year rate of local recurrence was 0.6% for patients receiving radiation plus tamoxifen and 7.7% for patients receiving tamoxifen alone (HR 8.3; $P < 0.001$). The 5-year disease-free survival rates were 91% for patients receiving radiation and tamoxifen versus 84% for patients receiving tamoxifen alone ($P = 0.004$). In a planned subset analysis of women with the most favorable-risk disease, the 5-year rate of local recurrence of women with estrogen receptor-positive tumors measuring 2 cm or less was 0.5% for patients receiving radiation and tamoxifen and 5.9% for patients receiving tamoxifen alone ($P < 0.001$). The 5-year rate of axillary recurrence was also less with radiation versus no radiation (0.5 versus 2.5% ($P = 0.049$), respectively). Overall survival and distant recurrence rates were not statistically different between groups.

The most recent study evaluating the role of radiation omission in patients with low-risk invasive breast cancer is the PRIME II which enrolled 1326 women in the United Kingdom, Greece, Australia, and Serbia from 2003 to 2009 [28]. All women were 65 years or older and had low-risk disease defined as node-negative, hormone receptor-positive breast cancer measuring 3 cm or less. The study allowed for tumors with lymphovascular invasion or nuclear grade 3 histology, but not both. Following surgical axillary staging and breast-conserving surgery with pathologic margins of 1 mm or more, patients were randomized to receive endocrine therapy and whole-breast irradiation with a boost or endocrine therapy alone. The 5-year rate of ipsilateral breast tumor recurrence was 4.1% in the endocrine therapy alone arm and 1.3% in the endocrine therapy plus radiation arm. The hazard ratio for ipsilateral breast tumor recurrence for the endocrine therapy alone arm was 5.19 ($P = 0.0007$). Five-year overall survival was 93.9% in both treatment arms. Regional recurrence, distant metastases, contralateral breast cancers, and new breast cancers were not significantly different between groups. Analysis of patient characteristics showed 88% of patients had tumors 2 cm or smaller with roughly 40% of tumors measuring 1 cm or less. In more than half of patients, the surgical margin was either greater than 5 mm or re-excision was performed. Ninety percent of patients had estrogen receptor-rich tumors, and more than 95% of patients had tumors of low or intermediate grade.

Collectively these studies suggest the local control benefit of adjuvant radiation for elderly patients with low-risk features is statistically significant, but the absolute value may be relatively small. Adjuvant radiation for this subgroup of patients has not been shown to improve overall survival or distant metastasis-free survival. The decision to give radiation to these patients must weigh improvement in local recurrence against the overall risk of disease recurrence and the risk of radiation treatment side effects. Patient longevity must also be considered because the cumulative risk of disease recurrence increases over time so patients with a long life expectancy will experience a higher risk of disease recurrence than patients with a shorter life expectancy.

Regional Nodal Irradiation in Breast-Conserving Therapy

Whole-breast irradiation often includes treatment of level 1 and part of level 2 axillary lymph nodes. The addition of regional nodal irradiation expands the treated nodal basins to include level 3 axillary nodes, supraclavicular nodes, and internal mammary nodes. The addition of regional nodal radiation to whole-breast radiation typically occurs when encountering positive axillary lymph nodes and its role in breast-conserving treatment has historically been extrapolated from trials evaluating locoregional radiotherapy in the postmastectomy setting. Two recently published randomized trials have explored the benefit of regional nodal radiotherapy in the setting of breast conservation and whole-breast radiotherapy. Although the results are supportive of a benefit of regional nodal irradiation in high-risk or node-positive patients, the relative benefit is small and the trials have generated discussion regarding how to best identify those patients who will receive a meaningful benefit from added therapy in both the breast conservation and postmastectomy scenarios. The NCIC (National Cancer Institute of Canada) Clinical Trials Group MA.20 trial evaluated the benefit of regional nodal irradiation in node-positive or high-risk early-stage invasive breast cancer patients treated with breast-conserving surgery and adjuvant chemotherapy [29]. Eligible patients underwent breast-conserving surgery and axillary staging with sentinel lymph node biopsy or axillary dissection. Patients were required to have positive axillary nodes on pathologic review or have a pathologically negative axilla, but have high-risk features. High-risk features included a primary breast tumor measuring at least 5 cm, or a breast tumor measuring at least 2 cm with fewer than ten axillary nodes removed and at least one of the following: estrogen receptor negativity, grade 3 histology, or lymphovascular invasion. Following surgery, patients received adjuvant chemotherapy, endocrine therapy, or both. The study enrolled 1832 eligible patients who were randomized to adjuvant whole-breast irradiation (control arm) or adjuvant whole-breast and regional nodal irradiation which included treatment of the internal mammary, supraclavicular, and axillary lymph nodes. The radiation dose was 50 Gy given over 25 fractions. Ninety-nine percent of patients had T1 or T2 disease and 75% of patients had estrogen receptor-positive tumors. Two-thirds of patients had ten or more axillary lymph nodes removed. Half of patients had one pathologically positive node, and three-fourths of patients had one or two positive nodes. At 10 years of follow-up, the primary outcome of overall survival was not statistically different between groups, 81.8% in the whole-breast irradiation group and 82.8% in the whole-breast and regional nodal irradiation group (HR 0.91; $P = 0.38$). Disease-free survival was improved with regional nodal irradiation compared to whole-breast irradiation (82 versus 77%; HR 0.76; $P = 0.01$). Regional nodal irradiation also improved 10-year isolated locoregional disease-free survival compared to whole-breast-only irradiation (95.2 versus 92.2%; HR 0.59; $P = 0.009$) and 10-year distant disease-free survival (86.3 versus 82.4%; HR 0.76; $P = 0.03$). Breast cancer-specific mortality did not differ statistically between groups. On preplanned subgroup analysis of patients with estrogen receptor-negative disease, regional nodal irradiation improved 10-year overall survival compared to whole-breast-only irradiation (81.3 versus 73.9%; HR 0.69; $P = 0.05$).

The European Organization for Research and Treatment of Cancer (EORTC) 22922/10925 trial enrolled 4004 women in 13 countries to evaluate the survival benefit of elective internal mammary and medial supraclavicular irradiation in patients with stage I, II, or III invasive breast cancer [30]. Patients were eligible if their primary breast tumor was centrally or medially located, with or without axillary nodal involvement, or if the primary breast tumor was externally located with axillary nodal involvement. Following mastectomy or breast-conserving surgery, patients were randomized to elective radiation to the internal mammary and medial supraclavicular nodal basins or no radiation treatment to these nodal basins. Most patients (76%) underwent breast-conserving surgery followed by whole-breast irradiation, and 85% received a tumor bed boost. A minority of patients (24%) underwent mastectomy of which approximately three-fourths received chest wall irradiation. Systemic therapy was given to almost all node-positive patients (99%) and to two-thirds of node-negative patients. The axillary disease burden was low in most patients with 44.5% of patients having no pathologically involved lymph nodes and 43% of patients having 1–3 pathologically involved nodes. Sixty percent of patients had a primary breast tumor 2 cm or smaller, and 36% of patients had a primary breast tumor measuring 2–5 cm. The median patient age was 54. Ten-year overall survival was borderline statistically different between groups, with an 82.3% overall survival rate in the elective nodal irradiation group and 80.7% in the group without elective nodal irradiation (HR 0.87; $P = 0.06$). Elective nodal radiation improved 10-year breast cancer mortality from 14.4 to 12.5% (HR 0.082; $P = 0.02$) and improved 10-year disease-free survival from 69.1 to 72.1% (HR 0.89; $P = 0.04$). Distant disease-free survival was also higher in the elective nodal irradiation group compared to no elective irradiation, 78 versus 75%, respectively (HR 0.86; $P = 0.02$).

Radiation Boost

A radiation boost is a short course of focused tumor bed irradiation additional to whole-breast irradiation. Studies have shown that a tumor bed boost improves local control, especially in younger patients.

The EORTC boost trial was a multicenter trial which examined the benefit of a lumpectomy cavity boost in 2657 patients with early-stage breast cancer [31]. Patients were eligible if they were age 70 or younger and had T1-T2 N0-1 M0 invasive breast cancer. Patients underwent axillary dissection and local excision of the primary breast tumor with a 1–2 cm margin. Patients with microscopically negative margins underwent whole-breast irradiation of 50 Gy over 5 weeks and were then randomized to a 16 Gy boost to the tumor bed or no boost. Overall survival at 20 years was not statistically different between groups with survival at 59.7% in the boost group compared to 61.1% in the no boost group (HR 1.05; $P = 0.323$). The boost group had decreased local recurrence as the first treatment failure compared to the no boost group (9 versus 13%) (HR 0.65; $P < 0.001$). Twenty-year ipsilateral breast tumor recurrence was 12.0% in the boost group compared to 16.4% in the no boost group. At 20 years, a higher rate of severe fibrosis was seen in the boost group compared to the no boost

group, 5.2 versus 1.8% ($P < 0.0001$). The absolute reduction in local recurrence provided by a boost was greatest in younger patients and progressively decreased in older subgroups of patients. For example, the boost decreased 20-year local recurrence in patients younger than age 40 from 36.0 to 24.4%, while in patients older than age 60, local recurrence decreased from 12.7 to 9.7%.

The Lyon Breast Cancer Trial also investigated the role of a tumor bed boost. The study enrolled 1024 patients less than 70 years of age with invasive ductal carcinoma measuring up to 3 cm [32]. All patients underwent breast-conserving surgery with negative pathologic margins followed by whole-breast irradiation of 50 Gy in 20 fractions. Patients were randomized to a 10 Gy boost to the tumor bed or no further treatment. With a median follow-up of 3.3 years, the 5-year rate of local recurrence was 3.6% in the patients who received a boost versus 4.5% in the patients who received no boost ($P = 0.044$). Although the rate of grade 1 or 2 telangiectasia was higher in the boost group (12.4 versus 5.9%), patient-reported assessment of cosmetic result was not different between treatment groups.

Hypofractionation

Traditionally, patients treated with whole-breast irradiation received 25–28 daily fractions (treatments) given at a dose of 1.8–2 Gy per day, potentially followed by a boost. Hypofractionation is treating patients with a fewer number of fractions than would traditionally take place usually with goal of reducing overall treatment duration. Hypofractionation typically involves giving patients a higher daily dose of radiation than one would receive with traditionally fractionated treatment. Hypofractionated treatment in breast cancer has reduced the number of whole-breast treatments from 25 to 28 fractions potentially followed by a boost to 15 or 16 fractions +/- a boost. This reduces treatment duration from 5–7 to 3–4 weeks.

The validity of hypofractionated whole-breast radiation treatment was established by three large randomized trials comparing hypofractionated to conventionally fractionated treatment. These trials suggest hypofractionated treatment provides equivalent local control and toxicity compared to traditionally fractioned treatment in appropriately selected patients.

The Ontario Clinical Oncology Group's hypofractionation trial was a multicenter trial in Canada which enrolled patients from April 1993 to September 1996 [29]. The trial included 1230 women with pathologically node-negative invasive breast cancer treated with lumpectomy. Patients were excluded if they had a tumor larger than 5 cm, clinical T4 disease, or breast width greater than 25 cm. Patients were randomized to whole-breast irradiation of 42.5 Gy in 16 fractions over 22 days or 50 Gy in 25 fractions over 35 days. Ten-year local recurrence was not significantly different between groups (6.2% in the 42.6 Gy group and 6.7% in the 50 Gy group). Ten-year overall survival was the same between groups (84%).

The START-A and START-B trials were multicenter hypofractionation trials which ran concurrently in the United Kingdom between 1999 and 2002 [33]. Eligible patients had pT1-T3a pN0-N1 M0 invasive breast cancer treated with

breast-conserving surgery or mastectomy. The majority of patients received tamoxifen and/or chemotherapy.

The START-A trial randomized 2236 patients to three different radiation treatment schedules, all given over 5 weeks: 39 Gy in 13 fractions, 41.6 Gy in 13 fractions, or 50 Gy in 25 fractions (control group) [33]. A sequential tumor bed boost was allowed as was treatment of the regional lymph nodes if lymph nodes were positive. Eighty-five percent of patients received breast-conserving surgery and 61% received a tumor bed boost; 29% of patients had positive lymph nodes and 14% received locoregional irradiation. At a median follow-up of 9.3 years, the 10-year rate of locoregional relapse did not differ statistically between the 41.6 and 50 Gy groups (6.3 versus 7.4%, respectively; HR 0.91; $P = 0.65$) or between the 39 and 50 Gy groups (8.8 versus 7.4%, respectively; HR 1.18; $P = 0.41$).

The START-B hypofractionation trial enrolled patients concurrently with the START-A trial. Similar to the START-A trial, eligible patients on START-B were women who had pT1-T3a pN0-N1 M0 invasive breast cancer treated with breast-conserving surgery or mastectomy [33]. A majority of patients received tamoxifen and/or chemotherapy. The START-B trial randomized 2215 patients to two different radiation treatment schedules with differing durations of treatment: 40 Gy in 15 fractions over 3 weeks (experimental group) or 50 Gy in 25 fractions over 5 weeks (control group). A sequential tumor bed boost was allowed. Ninety-two percent of patients received breast-conserving surgery and 43% received a tumor bed boost; 23% of patients had positive lymph nodes but only 7% underwent locoregional irradiation. At a median follow-up of 9.9 years, the 10-year rate of locoregional relapse was not significantly different between the 40 Gy group and the 50 Gy group (4.3 versus 5.5%; HR 0.65; $P = 0.21$).

In START-A trial, there was significantly less breast edema, telangiectasias, and moderate or marked breast induration in the 39 Gy group compared to the 50 Gy group; there was no significant difference in toxicity between the 41.6 and 50 Gy groups. In START-B, there was significantly less breast edema, breast shrinkage, and telangiectasia development in the 40 Gy group compared to the 50 Gy group.

In 2011, the American Society for Radiation Oncology issued an evidence-based guideline for fractionation for whole-breast irradiation [34]. The guideline stated that for patients aged 50 or older with pT1-T2 pN0 breast cancer treated with breast-conserving surgery without adjuvant chemotherapy, hypofractionated whole-breast irradiation provides equivalent local control and toxicity compared to conventional fractionated whole-breast irradiation. When using hypofractionation, they recommended the radiation dose along the central axis of the breast deviate no more or less than 7% from the prescription dose. The task force behind the guideline favored giving hypofractionated radiotherapy using a dose schedule of 42.5 Gy in 16 fractions when a boost is not used. There was no consensus regarding the use of a tumor bed boost with hypofractionation. Additionally, the task force recommended the heart should be excluded from the primary treatment fields when hypofractionated whole-breast radiation is used due to the uncertainty regarding late effects of hypofractionation on cardiac function.

In 2014, the American Society for Radiation Oncology, as part of its Choosing Wisely campaign, recommended that in women who are aged 50 years or older

with early-stage invasive breast cancer, whole-breast irradiation following breast-conserving surgery should not be given without consideration of shorter treatment schedules [35].

Accelerated Partial-Breast Irradiation

The previous sections have covered the literature supporting adjuvant whole-breast irradiation therapy as part of standard of care treatment after breast-conserving surgery, with hypofractionation shown to be a reasonable alternative to conventional fractionation in appropriately selected patients. However, whole-breast radiation therapy may be overtreating a significant volume of uninvolved breast tissue, and many hypothesize that this treatment of uninvolved tissue may be responsible for some of the acute and chronic toxicity associated with breast-conserving therapy. Accelerated partial-breast irradiation (APBI) has been investigated as a possible alternative to whole-breast radiation therapy for select patients with DCIS or low-risk invasive breast cancer [36]. The rationale behind APBI is that the majority of breast relapses occur within or near the tumor bed. Pathological studies from mastectomy specimens have demonstrated a lower probability of subclinical microscopic disease with increasing distance from the primary tumor [16, 36–40]. APBI targets only the surgical bed and a limited volume of normal tissue surrounding the surgical bed (Figs. 5.3 and 5.4). The accelerated treatment schedule reduces the overall radiation treatment duration to 1 week or less, which is more feasible for women with difficulty traveling to a radiation treatment center or women may not want to commit to the longer treatment duration associated with conventional or

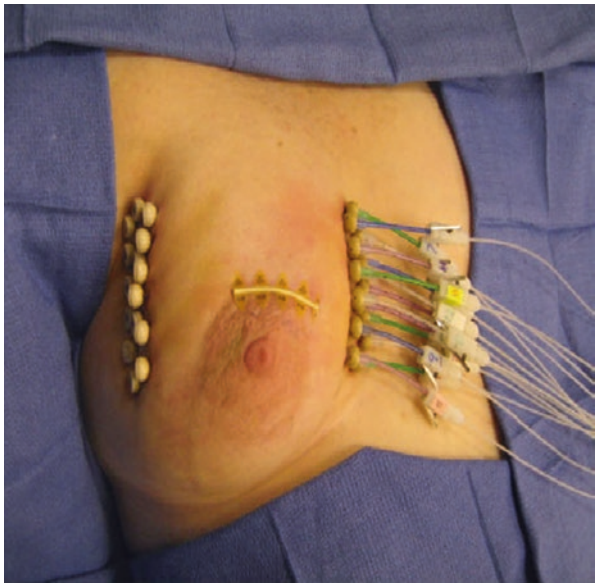

Fig. 5.3 External view of a multicatheter interstitial brachytherapy accelerated partial-breast irradiation treatment

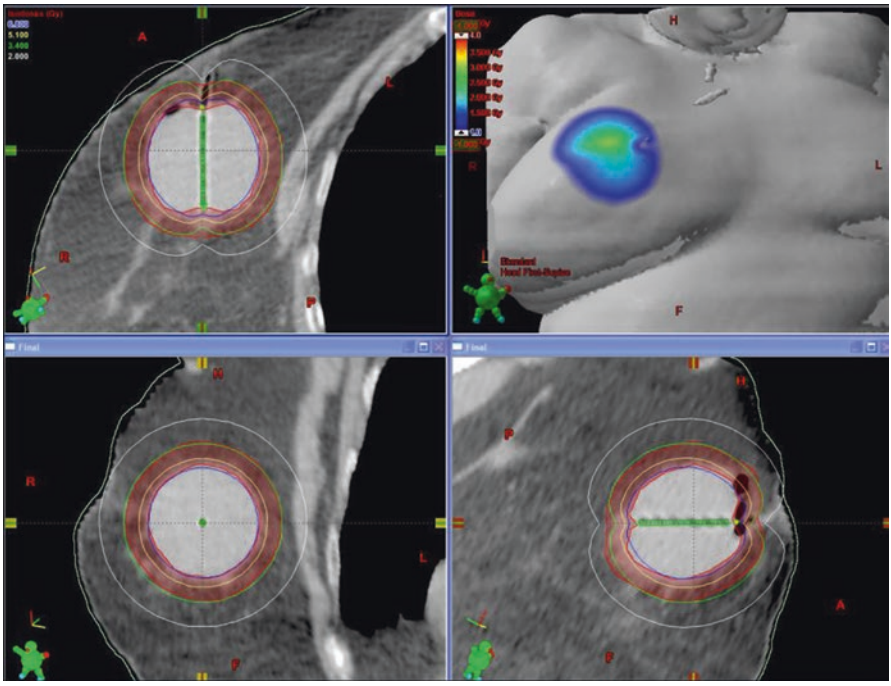

Fig. 5.4 Axial view, skin-rendering view, coronal view, and sagittal view of an intracavitary brachytherapy accelerated partial-breast irradiation treatment

hypofractionated whole-breast radiation. The advantages of APBI extend beyond convenience. APBI limits radiation exposure to only the part of the breast surrounding the tumor bed and can effectively minimize dose to the lungs, heart, chest wall, ribs, and normal breast or nodal tissue. APBI may also reduce certain radiation treatment-related toxicities, which may improve overall quality of life [41].

Historically, the first utilized APBI technique was multicatheter interstitial brachytherapy, which was primarily used as a boost technique after whole-breast irradiation [42, 43]. This technique involves the use of multiple catheters that are generally positioned at 1.0–1.5 cm intervals. The total number of catheters and planes employed is dependent on the size, extent, and shape of the tumor cavity. Multiple studies utilizing this technique have established multicatheter interstitial brachytherapy as an acceptable treatment option for appropriately selected patients [44–46]. Among partial-breast irradiation techniques, this technique has the longest patient follow-up, allowing for more accurate outcome analyses. However, it is both complex and technically challenging, limiting its widespread use.

Starting in 1998, the Hungarian National Institute of Oncology performed a prospective trial which enrolled 258 women with pT1 pN0-1mic, grade 1–2, non-lobular breast cancer resected with negative margins and randomized participants to conventionally fractionated whole-breast irradiation to 50 Gy in 2 Gy fractions (n = 130) or partial-breast irradiation. Partial-breast irradiation was delivered with HDR

interstitial brachytherapy to a dose of 36.4 Gy given over seven twice-daily fractions of 5.2 Gy ($n = 88$) or electrons to a dose of 50 Gy in 2 Gy fractions ($n = 40$) [1]. With 10 years of follow-up, there was no statistical difference in local recurrence between whole-breast irradiation group and the partial-breast irradiation groups (5.9 vs. 5.1%, respectively; $p = 0.77$). Overall survival, disease-free survival, and cause-specific survival did differ between treatment arms. However, there was an improved good-excellent cosmetic outcome with partial-breast irradiation techniques.

From 2004 to 2009, the Groupe European de Curietherapie—European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) conducted a multi-institutional, multinational, phase III, non-inferiority trial which randomized 1184 early-stage breast cancer patients to whole-breast irradiation or accelerated partial-breast irradiation using multicatheter interstitial brachytherapy [47]. Eligible patients had unifocal and unicentric stage 0, I, or IIa breast cancer (lesions ≤3 cm, pN0 or N1mi) treated with breast-conserving surgery with at least 2 mm margins. Whole-breast irradiation ($n = 551$) was prescribed to a dose of 50–50.4 Gy given in 1.8–2 Gy fractions followed by a 10 Gy boost. Accelerated partial-breast irradiation using a multicatheter interstitial technique was delivered using twice-daily high-dose rate brachytherapy to a dose of 32.0 Gy given in 8 fractions (8 × 4.0 Gy) or 30.3 Gy in 7 fractions (7 × 4.3 Gy), or pulsed-dose rate brachytherapy to a dose of 50 Gy with pulses of 0.60–0.80 Gy/h (1 pulse per hour, 24 h/day). The 5-year rate of local recurrence was 0.9% for the whole-breast irradiation group and 1.4% for the accelerated partial-breast irradiation group ($p = 0.42$) with the accelerated partial-breast technique being statistically non-inferior to whole-breast irradiation at 5 years. There was also no difference in the 5-year rates of grade 2–3 late skin side effects, grade 2–3 subcutaneous tissue late side effects, or grade 3 fibrosis. No patients experienced grade 4 toxicity.

Intracavitary brachytherapy is a less complex partial-breast technique with increased reproducibility. It has become the most widely used brachytherapy technique for APBI. The technique employs a single-balloon catheter introduced into the lumpectomy site either at the time of lumpectomy or percutaneously after surgery (Fig. 5.5). The catheter is located centrally within a distal balloon which is inflated after the catheter is placed in the lumpectomy cavity. Correct placement requires symmetry of the balloon, conformance of the balloon surface to the lumpectomy cavity, and a minimum distance between the surface of the balloon and skin of >5 mm (ideally >7 mm). Like the multicatheter technique, treatment is frequently delivered via an HDR remote afterloading system to a circumferential 1 cm distance from the balloon surface.

External beam APBI represents a noninvasive alternative with multiple techniques available. Three-dimensional conformal radiotherapy (3D-CRT) was the initial technique. Challenges with this technique include daily positioning of the target, movement with breathing, and delivery of higher doses to the surrounding normal breast tissue than with brachytherapy. Nonetheless, this approach has been widely embraced and has been shown to be reproducible [48, 49]. However, concerns regarding cosmesis and toxicity have emerged in more recent trials [50, 51]. The RAPID trial enrolled 2135 women (age > 40 years, tumor <3 cm) who underwent 3D-CRT APBI or hypofractionated whole-breast irradiation. Interim analysis demonstrated increased adverse cosmesis and grade

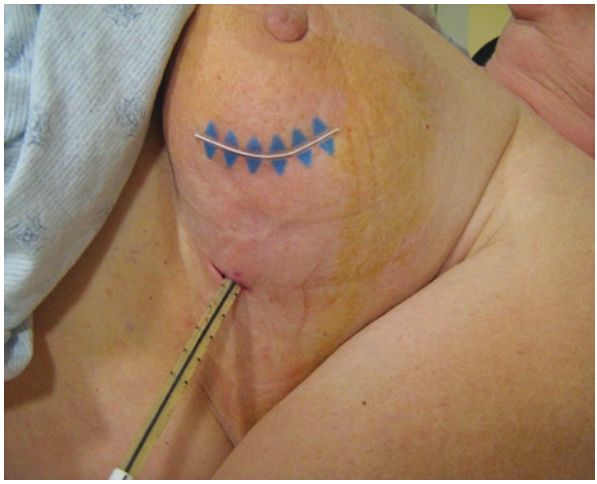

Fig. 5.5 External view of an intracavitary brachytherapy accelerated partial-breast irradiation treatment. A balloon attached to the end of the catheter is located within the lumpectomy cavity

1 and 2 toxicities with 3D-CRT APBI at 3 years [52]. Recent data supports the use of IMRT (intensity modulated radiation therapy) rather than 3D-CRT to deliver external beam APBI [53]. A University of Florence trial included 520 patients (age > 40 years, tumor size ≤2.5 cm) who received APBI via IMRT (30 Gy given over 5 fractions delivered every other day) or conventionally fractionated whole-breast irradiation. With 5-year follow-up, IMRT APBI showed reduced toxicity and improved cosmetic outcome compared to whole-breast treatment, with no difference in local control [54].

Intraoperative ABPI is a technique that has been studied primarily outside of the United States. Radiation is delivered in a single intraoperative dose to the lumpectomy site at the time of surgery using intraoperative electrons or intraoperative photons. TARGIT-A was a phase III, non-inferiority study which randomized over 3451 women to either targeted intraoperative radiation (TARGIT) or conventional whole-breast irradiation from 2000 to 2012 [55]. Per protocol, approximately 15% of patients receiving TARGIT also received whole-breast radiation because of unexpected adverse features seen on final pathology. Targeted intraoperative radiation was given to a dose of approximately 20 Gy at the tumor bed surface with the radiation dose decreasing to approximately 5–7 Gy at 1 cm from the tumor bed surface. At last reporting, 1222 patients had a median follow-up of 5 years. The 5-year risk of local recurrence was 3.3% for TARGIT and 1.3% for whole-breast irradiation (p = 0.042) [55]. There was no difference in complications between the two groups.

Postmastectomy Radiation

Indications for Postmastectomy Radiation for Invasive Breast Cancer

1. Patients with one or more pathologically positive lymph nodes evaluated at surgery or prior to neoadjuvant chemotherapy
2. Positive mastectomy surgical margin or mastectomy surgical margin of <1 mm
3. Tumor size >5 cm
4. Inflammatory breast cancer

Benefit of Postmastectomy Radiation

For patients with node-positive disease, postmastectomy radiation improves locoregional recurrence-free survival, recurrence-free survival, breast cancer-specific survival, and overall survival.

Patients Who May Avoid Postmastectomy Radiation

Patients with negative axillary lymph nodes and primary breast tumor 5 cm less with mastectomy margin 1 mm or greater

Absolute Contraindication

Pregnancy

Relative Contraindications

Active scleroderma or lupus involving the skin, previous radiation

Factors for Consideration

Patient age, patient life expectancy, comorbidities which may increase the risk of complications, tumor size, margin width, lymphovascular space invasion, number of lymph nodes involved, volume of lymph node involvement, extranodal extension, number of lymph nodes removed, tumor grade, tumor histology, hormone receptor status, HER2/neu status, response to neoadjuvant chemotherapy, cosmetic result, and patient expectations

Radiation Technique

Most patients receiving postmastectomy radiation should receive treatment to the chest wall and comprehensive regional nodes which includes the undissected axilla, supraclavicular-axillary apical nodes, and internal mammary nodes. Less extensive fields may be indicated for a subset of patients with a lower risk of recurrence at the discretion of the treating radiation oncologist. Postmastectomy radiation is given with external beam irradiation. The dose for postmastectomy radiation is 50 Gy in 25–28 fractions. A boost of 10–16 Gy may be added at the discretion of the treating radiation oncologist.

Selected Studies

Survival Improvement of Patients with Positive Lymph Nodes

The survival advantage of postmastectomy radiation for node-positive breast cancer patients was established by three modern postmastectomy radiation trials and a large meta-analysis.

The earliest of the modern postmastectomy radiation trials was performed by the British Columbia Cancer Agency in Vancouver and Victoria, British Columbia. From January 1979 to December 1986, the trial enrolled 318 premenopausal women with pathologically involved axillary lymph nodes [56]. The patients were treated

with modified radical mastectomy followed by adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy. Patients were randomized to adjuvant locoregional radiation or no additional treatment. Radiation was targeted to the postmastectomy chest wall, supraclavicular lymph nodes, axillary lymph nodes, and bilateral internal mammary lymph nodes. Radiation treatment took place between the fourth and fifth cycles of chemotherapy. A dose of 37.5 Gy in 16 fractions was given to the chest wall, 35 Gy in 16 fractions to the supraclavicular and axillary lymph nodes, and 37.5 Gy in 16 fractions to the bilateral internal mammary lymph nodes. At 20-year follow-up (median follow-up of 249 months), the radiation group had significantly better isolated locoregional recurrence-free survival compared to the no additional treatment group (90 versus 74%; RR 0.36; $P = 0.002$) and better systemic relapse-free survival (48 versus 31%; RR 0.66; $P = 0.004$). The radiation group showed higher rates of breast cancer-free survival (48 versus 30%; RR 0.63; $P = 0.001$), event-free survival (35 versus 25%; RR 0.70; $P = 0.009$), and breast cancer-specific survival (53 versus 38%; RR 0.67; $P = 0.008$). Overall survival increased by 10% with radiation (47% with radiation versus 37% without radiation) (RR 0.73; $P = 0.03$).

The Danish Breast Cancer Cooperative Group protocol 82b enrolled 1708 high-risk premenopausal women from November 1982 to December 1989 [57]. High risk was defined as axillary lymph node involvement, tumor size greater than 5 cm, or breast cancer invasion into the skin or pectoral fascia. Patients were in pathologic stage II or III. All patients were treated with total mastectomy and axillary nodal dissection, with a median of seven lymph nodes removed. Following surgery, patients were randomized to receive 9 weeks of CMF chemotherapy alone or an 8-week split course of CMF chemotherapy with locoregional radiation occurring during the split. A third group received CMF plus tamoxifen, but enrollment was discontinued in June 1986 because of greater than expected mortality in this group. Radiation consisted of treatment to the chest wall, surgical scar, and regional lymph nodes (supraclavicular, infraclavicular, axillary, and internal mammary lymph nodes). The radiation dose was 50 Gy in 25 fractions given over 5 weeks or 48 Gy in 22 fractions given over 5½ weeks. At 10-year follow-up (median 114 months), there was improved locoregional recurrence in the group receiving CMF plus radiation compared to the group receiving CMF alone (9 versus 32%, $P < 0.001$). Disease-free survival was increased in the chemotherapy plus radiation group compared to the chemotherapy alone group (40 versus 34%, $P < 0.001$). Overall survival was higher with CMF plus radiation compared to CMF alone (54 versus 45%, $P < 0.001$). On multivariate analysis, postmastectomy radiation increased disease-free survival and overall survival regardless of tumor size, number of positive of nodes, or tumor grade.

The Danish Breast Cancer Cooperative Group protocol 82c included 1460 postmenopausal high-risk breast cancer patients with high-risk indicating axillary lymph node involvement, tumor size great than 5 cm, or cancer invasion into the skin or pectoral fascia [58]. Trial enrollment occurred between October 1982 and March 1990. Like Danish 82b, patients were treated with mastectomy and axillary lymph node dissection with a median of seven lymph nodes removed. Danish 82c

randomized patients to adjuvant radiation plus 1 year of tamoxifen or 1 year of tamoxifen alone. A third group received adjuvant CMF plus tamoxifen and was reported separately. Radiation was targeted to the chest wall, surgical scar, and regional lymph nodes (supraclavicular, infraclavicular, axillary, and internal mammary lymph nodes). The radiation dose was 50 Gy in 25 fractions over 35 days or 48 Gy in 22 fractions over 38 days. At 10 years of follow-up (median 119 months), the trial results showed improved locoregional recurrence in the radiation plus tamoxifen group compared to the tamoxifen alone group (8 versus 35%, $P < 0.001$). Total recurrences were fewer in the radiation plus tamoxifen group compared to tamoxifen alone (47 versus 60%), and disease-free survival was better with radiation plus tamoxifen compared to tamoxifen alone (36 versus 24%, $P < 0.001$). Overall survival was increased with radiation plus tamoxifen compared to tamoxifen alone (45 versus 36%, $P = 0.03$).

In 2006, the Danish Breast Cancer Cooperative Group published a study of the long-term patterns of disease recurrence for 3083 patients enrolled in protocols 82b and 82c [59]. The 18-year probability of any first breast recurrence was 73% for patients who did not receive adjuvant radiation versus 59% for patients who received adjuvant radiation ($P < 0.001$). The probability of locoregional recurrence at 18 years was 49% for patients who did not receive adjuvant radiation versus 14% for patients who received adjuvant radiation ($P < 0.001$). The 18-year probability of distant metastases after locoregional recurrence was 35% for patients who did not receive adjuvant radiation versus 6% for patients who received adjuvant radiation ($P < 0.001$), and the probability of distant metastases was 64% for the no radiation group versus 53% for the radiation group.

In 2014 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis of individual patient data of 8135 women treated with mastectomy and axillary surgery in 22 clinical trials which took place from 1964 to 1986 [60]. It compared the outcomes of patients treated without radiation to patients treated with postmastectomy radiation to the chest wall and regional lymph nodes. Axillary surgery consisted of axillary dissection or axillary sampling. Axillary dissection was defined as dissection of levels I and II or a median of ten or more lymph nodes removed, and axillary sampling was defined as removal of less than levels I and II or less than a median of ten lymph nodes removed. The primary outcomes were 10-year locoregional recurrence, 10-year any first recurrence, 20-year breast cancer mortality, and 20-year overall mortality. Recurrence was analyzed at 10 years because many trials did not follow patients for recurrence beyond year 10.

The meta-analysis showed that for the 700 women who had pathologically negative lymph nodes after mastectomy and axillary dissection, postmastectomy radiation did not improve rates of locoregional recurrence, any first recurrence, or breast cancer mortality [60].

For the 3131 women with pathologically positive lymph nodes after mastectomy and axillary dissection, postmastectomy radiation improved locoregional recurrence from 26.0 to 8.1%, any first recurrence from 62.5 to 51.9%, and breast cancer mortality from 66.4 to 58.3%. Radiation decreased overall mortality from 70.4 to 65.4% [60].

For the 1314 women with 1–3 pathologically positive lymph nodes who were treated with mastectomy and axillary dissection, postmastectomy radiation decreased locoregional recurrence from 20.3 to 3.8%, any first recurrence from 45.7 to 34.2%, and breast cancer mortality from 50.2 to 42.3% [60]. For the 1772 women with four or more positive lymph nodes treated with mastectomy and axillary dissection, postmastectomy radiation improved locoregional recurrence from 32.1 to 13%, any first recurrence from 75.1 to 66.3%, and breast cancer mortality from 80.0 to 70.7% [60].

The benefit of postmastectomy radiation was sustained even if women received systemic therapy. For the 1133 women with 1–3 pathologically involve lymph nodes who were treated with mastectomy, axillary dissection, and systemic therapy, radiation decreased locoregional recurrence from 21.0 to 4.3%, any first recurrence from 45.5 to 33.8%, and breast cancer mortality from 49.4 to 41.5% [60]. For the 1677 women with four or more positive lymph nodes who were treated with mastectomy, axillary dissection, and systemic therapy, postmastectomy radiation improved locoregional recurrence from 31.5to 13.6%, any first recurrence from 74.0 to 65.8%, and breast cancer mortality from 78.0 to 70.0% [60].

There has been controversy whether radiation is needed if axillary dissection is performed and only one lymph node is pathologically involved. For the 318 women who had one pathologically positive lymph node and who were treated with mastectomy, axillary dissection, and systemic therapy, postmastectomy radiation improved locoregional recurrence from 20.2 to 3.0%, any first recurrence from 36.3 to 25.3%, and 15-year breast cancer mortality from 35.2 to 30.5% [60]. For the 365 women with 2–3 pathologically positive nodes who were treated with mastectomy, axillary dissection, and systemic therapy, postmastectomy radiation decreased locoregional recurrence from 19.3 to 4.7%, any first recurrence from 47.8 to 40.4%, and 15-year breast cancer mortality from 50.5 to 42.5%.

Overall the study showed that for women with node-positive disease who received postmastectomy radiation, one breast cancer death was prevented at 20 years for every 1.5 recurrences prevented at 10 years [60].

The American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology issued a focused guideline update on postmastectomy radiation in 2016 [61]. There was unanimous agreement on the panel that for patients with T1-T2 tumors and 1–3 positive axillary lymph nodes who undergo axillary nodal dissection, postmastectomy radiation reduces the risk of locoregional failure, any recurrence, and breast cancer mortality. They indicated that for subsets of patients with a very low risk of locoregional failure, the absolute benefit of postmastectomy radiation may be outweighed by the potential toxicity; however, the panel could not clearly define those subsets. The panel recommended consideration of the following factors in deciding whether or not a patient will benefit from postmastectomy radiation: patient age, limited life expectancy, comorbidities which may increase the risk of complications, tumor size, lymphovascular invasion, number of lymph nodes involved, size of lymph node involvement, response to neoadjuvant systemic therapy, tumor grade, and strong hormonal sensitivity. The panel recommended that postmastectomy radiation be given to patients

with axillary nodal involvement who receive neoadjuvant systemic therapy and have less than a pathological complete response. For clinically node-negative patients who receive neoadjuvant systemic therapy or those with a pathological complete response in the lymph nodes after neoadjuvant systemic therapy, the panel felt there was insufficient evidence to either recommend postmastectomy radiation or recommend omission of postmastectomy radiation. They recommended these patients be enrolled in clinical trials.

Neoadjuvant Chemotherapy

Traditional predictive factors such as tumor size, tumor grade, number of lymph nodes involved, volume of lymph node involvement, and extracapsular extension have been used by radiation oncologists to estimate the benefit of postmastectomy radiation and determine the appropriateness of postmastectomy radiation treatment. Because neoadjuvant chemotherapy can dramatically change one or all of these factors and introduce new predictive factors (such as pathological complete response), estimating the benefit of postmastectomy radiation after neoadjuvant chemotherapy is more difficult. There are no published randomized trials evaluating the role of postmastectomy radiation following neoadjuvant chemotherapy. However, there is retrospective analysis of patients treated prospectively on chemotherapy clinical trials. Presently there is insufficient evidence to suggest traditional predictive factors used to make postmastectomy radiation decisions are no longer beneficial or new predictive factors, such as pathological complete response, are equally or more predictive than traditional factors in making postmastectomy radiation treatment decisions. This is being evaluated on clinical trials such as NSABP B-51. Until the results of NSAB B-51and similar trials are published, postmastectomy radiation treatment decisions off clinical trial should be made using traditional predictive factors. Since these predictive factors may be altered by neoadjuvant chemotherapy, they should be determined using pretreatment workup and staging.

Huang et al. conducted a retrospective analysis of 744 patients enrolled on 6 consecutive prospective clinical trials at MD Anderson Cancer Center between 1974 and 2000 [62]. Patients had nonmetastatic, noninflammatory breast cancer and received doxorubicin-based chemotherapy and mastectomy. Outcomes from 542 patients who received postmastectomy radiation were compared to 134 patients who did not receive postmastectomy radiation. The study demonstrated that postmastectomy radiation reduced the rate of 10-year locoregional recurrence from 22 to 11%. On subset analysis, postmastectomy radiation significantly reduced the rate of locoregional recurrence for subsets of patients with clinical T3 or T4 tumors, stage IIB or greater disease, pathologic tumor size greater than 2 cm, and four or more positive lymph nodes. For patients with stage III or IV disease who achieved a pathological complete response after neoadjuvant chemotherapy, postmastectomy radiation reduced the rate of 10-year locoregional recurrence from 33 to 3%.

Postmastectomy radiation also improved 10-year cause-specific survival in patients with stage IIIB or greater disease (44 vs. 22%), clinical T4 tumors (45 vs. 24%), or four or more positive lymph nodes (44 vs. 18%). Overall survival was higher with postmastectomy radiation in patients with stage IIIB or greater disease (42 vs. 20%), clinical T4 tumors (42 vs. 20%), or four or more positive lymph nodes (38 vs. 15%).

Mamounas et al. performed a combined analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) trials B-18 and B-27 to determine the patterns and predictors of locoregional recurrence for patients treated with neoadjuvant chemotherapy [63]. In the two NSABP trials, patients who underwent lumpectomy after neoadjuvant chemotherapy received radiation to the breast alone, and patients who underwent mastectomy after neoadjuvant chemotherapy received no adjuvant radiation. In NSABP B-18, patients were randomized to receive neoadjuvant or adjuvant doxorubicin and cyclophosphamide (AC) given every 21 days for a total of four cycles. Patients aged 50 or older received tamoxifen for 5 years regardless of hormone receptor status. In NSABP B-27, patients were randomized to one of three treatment arms. Patients in group 1 received four cycles of neoadjuvant AC, patients in group 2 received four cycles of neoadjuvant AC followed by four cycles of neoadjuvant docetaxel given every 21 days, and patients in group 3 received four cycles of neoadjuvant AC followed by four cycles of adjuvant docetaxel. All patients received 5 years of tamoxifen regardless of hormone receptor status. In NSABP B-18, a total of 763 patients received adjuvant chemotherapy and 760 patients received neoadjuvant chemotherapy. All 2411 patients on NSABP B-27 received neoadjuvant chemotherapy. Mamounas performed a combined analysis of the 3171 patients who received neoadjuvant chemotherapy on the two trials. With 83 patients lost to follow-up, a total of 3088 patients were analyzed. Most patients in the trial had early-stage disease. In B-18, 65% of patients had clinical T1-2 N0 disease and 22% of patients had clinical T1-2 N1 disease. In B-27, 51% of patients had clinical T1-2 N0 disease and 20% of patients had clinical T1-2 N1 disease. Most patients were clinically node-negative; in B-18, 73% of patients were clinically node-negative; and in B-27, 70% of patients were clinically node-negative. On multivariate analysis of 1071 patients who were treated with mastectomy, independent predictors of 10-year locoregional recurrence were clinical tumor size greater than 5 cm versus less than 5 cm (HR 1.58), clinically node-positive versus node-negative (HR 1.53), pathological complete response in the breast versus no breast pathological complete response in node-negative patients (HR 2.21), and pathologically node-positive versus pathologically node-negative plus breast pathological complete response (HR 4.48).

In the 1890 patients who underwent lumpectomy, independent predictors of 10-year local regional recurrence on multivariate analysis included age 50 or older versus less than age 50 (HR 0.71), clinically node-positive versus node-negative (HR 1.70), pathological complete response in the breast versus no breast pathological complete response in node-negative patients (HR 1.44), and pathologically node-positive versus pathologically node-negative with breast pathological complete response (HR 2.25).

Table 5.1 Ten-year locoregional recurrence for patients treated with neoadjuvant chemotherapy followed by mastectomy without postmastectomy radiation [63]

	Clinically node negative		Clinically node positive	
	Tumor ≤5 cm	Tumor >5 cm	Tumor ≤5 cm	Tumor >5 cm
ypN(−)/breast pCR	6.6% ($n = 46$)	6.2% ($n = 16$)	0% ($n = 21$)	0% ($n = 11$)
ypN(−)/no breast pCR	6.3% ($n = 178$)	11.8% ($n = 95$)	10.8% ($n = 37$)	9.2% ($n = 84$)
ypN(+)	11.2% ($n = 184$)	14.6% ($n = 179$)	17.0% ($n = 143$)	22.4% ($n = 128$)

In general, the analysis showed a relatively low probability of locoregional recurrence for mastectomy patients who were clinically node-negative prior to neoadjuvant chemotherapy and pathologically node-negative after neoadjuvant chemotherapy. Locoregional recurrence was also low for patients who were clinically node-positive prior to neoadjuvant chemotherapy but had a pathological complete response in the breast and lymph nodes after neoadjuvant chemotherapy. Other subsets of patients had higher probabilities of locoregional recurrence. The incidence of locoregional recurrence at 10 years is summarized in Table 5.1 for mastectomy patients.

It is important to note that this analysis is a subset analysis of patients treated on two large chemotherapy clinical trials. Interpretation of the data is limited by many factors including the retrospective nature of the analysis, lack of a radiation treatment arm, small number of patients with a pathological complete response in the breast and lymph nodes, and most patients having early-stage, clinically node-negative disease. Patients with T4 or N2 disease at presentation were not eligible for treatment on either of the trials so this data does not apply to patients with more advanced disease. Furthermore, estrogen receptor, progesterone receptor, and HER2/neu status were not evaluated prior to chemotherapy, so these are not known for patients who had a pathological complete response in the breast and lymph nodes. Also, two different chemotherapy regimens were used, tamoxifen was given concurrently with chemotherapy rather sequentially, tamoxifen was given on the basis of age rather than ER status, and no patients received Herceptin. The greatest benefit of this analysis is hypothesis generation. This study and others led to the initiation of NSABP B-51. Table 5.2 highlights summary of radiation treatment recommendations at our institution.

Recurrent Disease

Patients with disease recurrence who did not previously receive radiation treatment are recommended to receive adjuvant radiation. Patients who previously received external beam irradiation may be eligible for re-irradiation with partial-breast radiation or external beam irradiation. Patients who previously received partial-breast irradiation may be eligible for re-irradiation with external beam irradiation.

Table 5.2 Summary of radiation treatment recommendations at VCU based on the above literature and acknowledging areas of controversy—this is how we do it.

Stage	Treatment recommendation
Mastectomy without neoadjuvant chemotherapy	
pT1/T2 N0 (positive or negative for ITC)	Observation is recommended if the surgical margins are negative. If the margins are positive, radiation to the chest wall and lower axilla is recommended.
pT1/T2 N1mic	If SLN biopsy only, radiation to the chest wall and lower axilla is recommended. If ALND (six nodes or more), observation is recommended if the surgical margins are negative. If the margins are positive, radiation to the chest wall and lower axilla is recommended.
pT1/T2 N1 with one node positive (macroscopic)	If SNL biopsy only, chest wall and regional nodal irradiation is recommended. If ALND (six nodes or more), observation may be considered if the patient has a less aggressive overall picture—e.g., older patients with small, low-grade, hormone receptor-positive, HER2-negative tumors resected with margins 2 mm or greater; otherwise chest wall and regional nodal irradiation is recommended.
pT1/T2 N1 with two nodes positive	Chest wall and regional nodal irradiation is recommended.
pT1/T2 N1 with three or more nodes positive	Chest wall and regional nodal irradiation is recommended.
pT3 N0	Chest wall and regional nodal irradiation is generally recommended. Observation may be considered for older patients with hormone receptor-positive, HER2-negative tumors measuring 5–6 cm and resected with good surgical margins.
pT4 N0 or inflammatory breast cancer	Chest wall and regional nodal irradiation is recommended.
Neoadjuvant chemotherapy followed by mastectomy	
Local regional irradiation is recommended for patients with evidence of preoperative nodal involvement until further evidence suggests otherwise. *Preoperative nodal evaluation includes imaging studies and/or biopsy	
cT1/T2 N1 with pCR in breast and nodes. N1 includes pathology or imaging.	Consider enrollment on NSABP B-51. Off protocol: chest wall and regional nodal irradiation is recommended. It is recognized that there is controversy regarding the role of radiation in this setting. Until this question is answered by randomized data, we recommend radiation.
cT1/T2 N1 with pCR in nodes but not in the breast	Consider enrollment on NSABP B-51. Off protocol: chest wall and regional nodal irradiation is recommended. It is recognized that there is controversy regarding the role of radiation in this setting. Until this question is answered by randomized data, we recommend radiation.
cT1/T2 N1 with pCR in the breast but not in nodes	Chest wall and regional nodal irradiation is recommended.
cT3/T4 or N2/N3	Chest wall and regional nodal irradiation is recommended regardless of response to chemotherapy.

(continued)

Table 5.2 (continued)

Stage	Treatment recommendation
Lumpectomy	
pT1/T2 N0 (positive or negative for ITC) or DCIS	For patients younger than age 70, breast irradiation is recommended. For patients aged 70–75, observation is acceptable for patients with small, hormone receptor-positive, HER2-negative tumors, with good surgical margins if the patient will receive 5 years of hormonal therapy. It is recognized that there is controversy whether the age for observation should be younger than 70. As new data arise and old data mature, the age for observation will likely decrease. Breast irradiation is recommended for patients who do not fit the criteria for observation. Breast irradiation may also be given to patients who meet the criteria for observation, but express a preference for radiation treatment to decrease the risk of local recurrence. For patients aged 75–80 or older, observation is preferred unless the patient has concerning prognostic factors or she is healthy and desires radiation treatment. As patient age increases, the preference for observation becomes greater.
pT1/T2 N1mic	Breast and lower axillary irradiation is recommended. Breast-only irradiation is recommended if the patient has undergone ALND (six nodes) or if the patient is older with a small, low-grade, hormone receptor-positive, HER2-negative tumor.
pT1/T2 N1 with one node positive	Whole-breast and regional nodal irradiation is recommended. Breast-only irradiation may be considered if the patient has undergone ALND (six nodes) and is older with a small, low-grade, hormone receptor-positive, HER2-negative tumor.
pT1/T2 with two nodes positive	Whole-breast and regional nodal irradiation is recommended.
pT1/T2 N1 with three or more nodes positive	Whole-breast and regional nodal irradiation is recommended.
pT3 N0	Whole-breast and regional nodal irradiation is generally recommended. Breast-only irradiation may be considered for older patients with low- or intermediate-grade, hormone receptor-positive, HER2-negative tumors measuring 5–6 cm.
Hypofractionation	
Hypofractionation (42.56 Gy in 16 fractions) is recommended if a patient meets all of the following criteria: 1. Patient is aged 50 years or older at diagnosis 2. Pathologic stage is T1-T2 N0 and patient has been treated with breast-conserving surgery 3. Patient has not been treated with systemic chemotherapy 4. The breast size is sufficiently small such that the central axis dose is no less than 93% and no greater than 107% of the prescription dose This recommendation may be revised as additional data becomes available (RTOG 1005). Patients who do not meet the criteria for hypofractionation should receive standard fractionation (50 Gy in 2 Gy fractions).	

Table 5.2 (continued)

Stage	Treatment recommendation
Boost	
Lumpectomy patients—a boost is recommended for: • All lumpectomy patients under age 60 • Any patient with surgical margins less than 2 mm • Any patient with aggressive features: – Node positivity – ER negativity and/or PR negativity – HER2 positivity – Grade 3 For patients treated with standard fractionation, the boost may be 10–16 Gy. For patients treated with hypofractionation, the boost may be 2.66 Gy × 4–6 fractions. Mastectomy patients: a boost is not recommended for reconstructed mastectomy patients who do not have close margins. A boost is otherwise at the discretion of the treating physician.	
Accelerated partial-breast irradiation	
We accept the American Brachytherapy Society's acceptable criteria for accelerated partial-breast irradiation.	
Criteria	
Age	≥50 years old
Size	≤3 cm
Histology	All invasive subtypes and DCIS
Estrogen receptor	Positive/negative
Surgical margins	Negative
Lymphovascular space invasion	Not present
Nodal status	Negative

References

1. Polgar C, Fodor J, Major T, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol. 2013;108(2):197–202. doi:10.1016/j.radonc.2013.05.008.
2. Shah C, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. Brachytherapy. 2013;12(4):267–77. doi:10.1016/j.brachy.2013.02.001.
3. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). J Am Coll Surg. 2009;209(2):269–77. doi:10.1016/j.jamcollsurg.2009.02.066.
4. Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol. 2001;28(4):400–18. doi:S0093775401001531 [pii].
5. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst. 2011;103(6):478–88. doi:10.1093/jnci/djr027.
6. Donker M, Litiere S, Werutsky G, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma in situ: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial. J Clin Oncol. 2013;31(32):4054–9. doi:10.1200/JCO.2013.49.5077.

7. Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol. 2006;45(5):536–43. doi:T673T26276376P0U [pii].
8. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12(1):21–9. doi:10.1016/S1470-2045(10)70266-7.
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr. 2010;2010(41):162–77. doi:10.1093/jncimonographs/lgq039.
10. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Syst Rev. 2013;11:CD000563. doi:10.1002/14651858.CD000563.pub7.
11. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer. 1996;77(11):2267–74. doi:10.1002/(SICI)1097--0142(19960601)77:113.0.CO;2-V [pii].
12. Silverstein MJ, Lagios MD. Treatment selection for patients with ductal carcinoma in situ (DCIS) of the breast using the University of Southern California/Van Nuys (USC/VNPI) prognostic index. Breast J. 2015;21(2):127–32. doi:10.1111/tbj.12368.
13. Wong JS, Chen YH, Gadd MA, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). Breast Cancer Res Treat. 2014;143(2):343–50. doi:10.1007/s10549-013-2813-6.
14. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol. 2015;33(7):709–15. doi:10.1200/JCO.2014.57.9029.
15. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol. 2015;33(33):3938–44. doi:10.1200/JCO.2015.60.8588.
16. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32. doi:10.1056/NEJMoa020989.
17. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233–41. doi:10.1056/NEJMoa022152.
18. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol. 2012;13(4):412–9. doi:10.1016/S1470-2045(12)70042-6.
19. Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol. 1996;14(5):1558–64. doi:10.1200/jco.1996.14.5.1558.
20. Sarrazin D, Le MG, Arriagada R, et al. Ten-year results of a randomized trial comparing a conservative treatment to mastectomy in early breast cancer. Radiother Oncol. 1989;14(3):177–84.
21. Liljegren G, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst. 1994;86(9):717–22.
22. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol. 2002;20(20):4141–9. doi:10.1200/JCO.2002.11.101.
23. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol. 2001;12(7):997–1003.
24. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087–106. doi:S0140-6736(05)67887-7 [pii].
25. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. 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. Lancet. 2011;378(9804):1707–16. doi:10.1016/S0140-6736(11)61629-2.
26. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382–7. doi:10.1200/JCO.2012.45.2615.
27. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004;351(10):963–70. doi:10.1056/NEJMoa040595.
28. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, PRIME II Investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015;16(3):266–73. doi:10.1016/S1470-2045(14)71221-5.
29. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015;373(4):307–16. doi:10.1056/NEJMoa1415340.
30. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med. 2015;373(4):317–27. doi:10.1056/NEJMoa1415369.
31. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47–56. doi:10.1016/S1470-2045(14)71156-8.
32. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol. 1997;15(3):963–8. doi:10.1200/jco.1997.15.3.963.
33. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013;14(11):1086–94. doi:10.1016/S1470-2045(13)70386-3.
34. Smith BD, Bentzen SM, Correa CR, et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011;81(1):59–68. doi:10.1016/j.ijrobp.2010.04.042.
35. Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: the American Society for Radiation Oncology's top 5 list. Pract Radiat Oncol. 2014;4(6):349–55. doi:10.1016/j.prro.2014.06.003.
36. Arthur DW, Vicini FA. Accelerated partial breast irradiation as a part of breast conservation therapy. J Clin Oncol. 2005;23(8):1726–35. doi:23/8/1726 [pii].
37. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet. 1991;338(8763):327–31. doi:0140-6736(91)90475-5 [pii].
38. Kurtz JM, Amalric R, Brandone H, et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. Cancer. 1989;63(10):1912–7.
39. Fowble B. Ipsilateral breast tumor recurrence following breast-conserving surgery for early-stage invasive cancer. Acta Oncol. 1999;38(Suppl 13):9–17.
40. Freedman GM, Anderson PR, Hanlon AL, Eisenberg DF, Nicolaou N. Pattern of local recurrence after conservative surgery and whole-breast irradiation. Int J Radiat Oncol Biol Phys. 2005;61(5):1328–36. doi:S0360-3016(04)02276-X [pii].
41. Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. J Natl Cancer Inst. 2000;92(3):269–71.
42. Kuske RR Jr. Breast brachytherapy. Hematol Oncol Clin North Am. 1999;13(3):543–58, vi–vii.
43. Vicini FA, Arthur DW. Breast brachytherapy: North American experience. Semin Radiat Oncol. 2005;15(2):108–15. doi:S1053429604001390 [pii].
44. Chen PY, Vicini FA, Benitez P, et al. Long-term cosmetic results and toxicity after accelerated partial-breast irradiation: a method of radiation delivery by interstitial brachytherapy for the treatment of early-stage breast carcinoma. Cancer. 2006;106(5):991–9. doi:10.1002/cncr.21681.

45. Shah C, Antonucci JV, Wilkinson JB, et al. Twelve-year clinical outcomes and patterns of failure with accelerated partial breast irradiation versus whole-breast irradiation: results of a matched-pair analysis. Radiother Oncol. 2011;100(2):210–4. doi:10.1016/j.radonc.2011.03.011.
46. Arthur DW, Winter K, Kuske RR, et al. A phase II trial of brachytherapy alone after lumpectomy for select breast cancer: tumor control and survival outcomes of RTOG 95-17. Int J Radiat Oncol Biol Phys. 2008;72(2):467–73. doi:10.1016/j.ijrobp.2007.12.056.
47. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229–38. doi:10.1016/S0140-6736(15)00471-7.
48. Baglan KL, Sharpe MB, Jaffray D, et al. Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). Int J Radiat Oncol Biol Phys. 2003;55(2):302–11. doi:S0360301602038117 [pii].
49. Shah C, Wilkinson JB, Lanni T, et al. Five-year outcomes and toxicities using 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Clin Breast Cancer. 2013;13(3):206–11. doi:10.1016/j.clbc.2012.09.020.
50. Hepel JT, Tokita M, MacAusland SG, et al. Toxicity of three-dimensional conformal radiotherapy for accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2009;75(5):1290–6. doi:10.1016/j.ijrobp.2009.01.009.
51. Liss AL, Ben-David MA, Jagsi R, et al. Decline of cosmetic outcomes following accelerated partial breast irradiation using intensity modulated radiation therapy: results of a single-institution prospective clinical trial. Int J Radiat Oncol Biol Phys. 2014;89(1):96–102. doi:10.1016/j.ijrobp.2014.01.005.
52. Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013;31(32):4038–45. doi:10.1200/JCO.2013.50.5511.
53. Lei RY, Leonard CE, Howell KT, et al. Four-year clinical update from a prospective trial of accelerated partial breast intensity-modulated radiotherapy (APBIMRT). Breast Cancer Res Treat. 2013;140(1):119–33. doi:10.1007/s10549-013-2623-x.
54. Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015;51(4):451–63. doi:10.1016/j.ejca.2014.12.013.
55. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014;383(9917):603–13. doi:10.1016/S0140-6736(13)61950-9.
56. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;97(2):116–26. doi:97/2/116 [pii].
57. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b trial. N Engl J Med. 1997;337(14):949–55. doi:10.1056/NEJM199710023371401.
58. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet. 1999;353(9165):1641–8. doi:S0140-6736(98)09201-0 [pii].
59. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol. 2006;24(15):2268–75. doi:JCO.2005.02.8738 [pii].

60. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383(9935):2127–35. doi:10.1016/S0140-6736(14)60488-8.
61. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. J Clin Oncol. 2016;34(36):4431–42. doi:10.1200/JCO.2016.69.1188.
62. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol. 2004;22(23):4691–9. doi:22/23/4639 [pii].
63. Mamounas EP, Anderson SJ, Dignam JJ, et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol. 2012;30(32):3960–6. doi:10.1200/JCO.2011.40.8369.