

Indications for adjuvant radiation therapy in breast cancer: a review of the evidence and recommendations for clinical practice

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Abstract: Radiation therapy (RT) plays an important role in the curative management of all stages of breast cancer. The optimal application of adjuvant RT is an area of continuous investigation, and the indications for treatment are refined with each new trial. This article reviews the evidence for adjuvant RT across five distinct clinical scenarios, with additional discussion of RT targets, techniques, and doses where appropriate.

Keywords: Breast cancer; clinical decision-making; radiation

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Introduction

In the last few years alone, several large randomized trials evaluating the use of radiation therapy (RT) in the treatment of breast cancer have been published and several more are in progress. The indications for RT evolve with each new trial result, and it can be difficult for clinicians to stay up-to-date on the standard of care. In this article, we review the evidence for adjuvant RT and provide recommendations in the context of five clinical scenarios: (I) ductal carcinoma in situ (DCIS); (II) non-locally advanced, node-negative breast cancer treated with up-front surgery; (III) non-locally advanced, node-positive breast cancer treated with up-front surgery; (IV) locally advanced and non-locally advanced node-positive breast cancer treated with neoadjuvant chemotherapy; and (V) inflammatory breast cancer (IBC). The term “locally advanced” is used herein to refer to patients with T3/4 and/or N2/3 tumors (e.g., tumor size >5 cm or involving skin or chest wall and/or ≥4 pathologically involved axillary lymph nodes or macrometastases to the internal mammary, infraclavicular, or supraclavicular nodal basins). The purpose of this article is to provide clinicians with a framework for making

adjuvant RT recommendations based on the current evidence.

Ductal carcinoma in situ (DCIS)

DCIS is a neoplastic process characterized by cytologically malignant, non-invasive ductal epithelial cells that are non-obligate precursors of invasive carcinoma. If left untreated, these tumors may transform into life-threatening invasive cancer. The goal of treatment is therefore to prevent progression to invasive disease, as well as rule out the presence of an invasive component at the time of diagnosis that may warrant more aggressive treatment (1).

The definitive treatment of pure DCIS includes a combination of surgery with or without RT and/or endocrine therapy. Historically, DCIS was treated with mastectomy, with low local recurrence rates of 1–3% (2). However, if a patient has no contraindications to RT and a breast-conserving surgery (BCS) can achieve negative margins, this surgical approach is also appropriate. This section will review the role of adjuvant RT in patients with DCIS.

Review of the evidence

BCS followed by whole breast irradiation (WBI) is a widely accepted alternative to mastectomy in the treatment of DCIS, though the two have never been directly compared. Randomized trials in DCIS have instead focused on comparing local excision with or without RT. In the 1980s and 1990s, four large randomized trials compared BCS with and without WBI, and findings consistently demonstrated that WBI decreased the rate of ipsilateral breast tumor recurrence (IBTR) by approximately 50%, though it had no effect on overall survival (OS) or distant metastasis-free survival (DMFS) (3-6). Further, an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of individual patient data from these four trials confirmed that adding RT to BCS halved the rate of ipsilateral breast events at 10 years (28% *vs.* 13%), but again had no effect on mortality (7). Interestingly, the magnitude of the effect of RT on local recurrence varied with age: women under age 50 experienced a relative risk reduction of 31%, while women age 50 and older experienced a relative risk reduction of 62%.

A subsequent trial from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-24) randomized patients treated with BCS and RT to adjuvant tamoxifen or placebo (8). At 5 years, the addition of tamoxifen reduced any breast event (inclusive of ipsilateral and contralateral events) from 13% to 8%. The benefit of tamoxifen on IBTR and contralateral breast events persisted at 10.5 years of follow-up but appeared limited to those with estrogen receptor (ER)-positive disease (9). This trial established RT plus tamoxifen as a reasonable standard of care following BCS.

Given the practical hardships and modest toxicities that accompany RT, investigators have long sought to identify a subgroup of DCIS patients for whom local excision alone is adequate. A phase II trial from the Eastern Cooperative Oncology Group (ECOG 5194) enrolled women in two strata: low or intermediate grade tumors measuring ≤ 2.5 cm or high grade tumors measuring ≤ 1 cm (10). Both groups were required to have surgical margins of ≥ 3 mm and no calcifications on post-operative mammogram. At a median follow-up of 6 years, the 5-year rate of ipsilateral breast events was 6% for the low to intermediate grade group and 15% for the high grade group. These rates continued to rise through 12 years, reaching 14% for the low to intermediate grade group and 25% for the high grade group, with no observed plateau (11).

To definitively determine if RT can be omitted in a highly selected group of low-risk patients, the Radiation Therapy Oncology Group (RTOG) conducted a large, multicenter randomized trial (RTOG 98-04) of adjuvant RT versus observation in "good risk" patients (12). The trial included 636 women with mammographically detected "good-risk" DCIS, defined as grade low to intermediate, size < 2.5 cm, and surgical margins ≥ 3 mm. Patients were randomized to adjuvant RT or observation; tamoxifen use was optional but common. At 7 years, the ipsilateral local failure rate in the observation arm was acceptably low at 6.7%; however the rate was reduced to just 0.9% in the group randomized to RT. Notably, tamoxifen was part of the treatment plan in 62% of patients, compared to 31% of patients in the ECOG 5194 study.

In all of the randomized trials of BCS with or without RT, RT was delivered to the whole breast, typically to a dose of 50 Gy in 25 fractions. A tumor bed boost was not recommended or not allowed in the SweDCIS, UK/ANZ, and RTOG 98-04 trials. In the NSABP B-17 and the European Organization for Research and Treatment of Cancer (EORTC) 10853 trials, a boost was delivered in 9% and 5% of patients, respectively. There are no randomized trials evaluating the use of a boost in DCIS, though many feel it is reasonable to add a boost based on the data from invasive cancer (discussed in the next section), particularly in younger women as the EBCTCG meta-analysis suggested only modest benefit from 50 Gy without a boost in this population.

Though WBI is the most standard approach for DCIS, accelerated partial breast (APBI) may be appropriate in select patients. APBI is a therapeutic approach that delivers focused RT to the area of the tumor bed, as this is the most common site of recurrence. APBI can be delivered with brachytherapy or with external beam RT, and is commonly given in 10 twice-daily fractions. DCIS patients > 45 years old with tumors ≤ 3 cm and negative surgical margins are considered candidates for APBI according to the American Society of Breast Surgeons consensus statement (www.breastsurgeons.org), though some of these features are considered "cautionary" or "unsuitable" according to the American Society for Radiation Oncology (ASTRO) consensus statement (13).

Summary and recommendations

- (I) Adjuvant WBI reduces IBTR after BCS for patients with DCIS. This risk is further reduced with the

- addition of tamoxifen;
- (II) RTOG 98-04 has identified a group of patients with an especially low risk of local recurrence after BCS alone, though RT still provides a statistically significant local control benefit;
 - (III) In low-risk patients, the small absolute benefit of adding RT should be weighed against comorbid illness, safety of RT delivery, availability of salvage options, and, most importantly, patient preference;
 - (IV) The roles of hypofractionation and tumor bed boost in DCIS are not clearly defined, though both are considered acceptable based on the data from invasive breast cancer;
 - (V) APBI may be appropriate in carefully selected patients, though suitability criteria vary across professional organizations.

Non-locally advanced, node-negative breast cancer treated with up-front surgery

For patients with non-locally advanced, node-negative breast cancer, up-front surgery is the most common treatment approach. Surgical options for management of the primary tumor include total mastectomy or BCS; options for evaluating the axilla include sentinel lymph node biopsy (SLNB; preferred in clinically node-negative patients) or axillary lymph node dissection (ALND). This section will discuss the role of adjuvant RT in patients who are clinically and pathologically node-negative.

Review of the evidence

A number of phase III randomized trials have demonstrated equivalent disease-free survival (DFS) and OS for patients treated with mastectomy versus BCS followed by RT (14-19). The largest of these studies was the NSABP B-06 trial, which randomized 1,851 women with stage I or II breast cancer to one of three arms: (I) total mastectomy; (II) lumpectomy alone; or (III) lumpectomy followed by 50 Gy of RT (14). At 20-year follow-up, there were no statistically significant differences between the groups in terms of DFS, OS, or DMFS. The addition of RT to lumpectomy reduced the cumulative incidence of IBTR from 39% to 14%.

Subsequent randomized trials of BCS with or without RT corroborated the findings of NSABP B-06 in that RT consistently reduced the rate of IBTR by approximately two-thirds (20-23). The benefit of RT persisted even in the setting of adjuvant endocrine therapy for small tumors, as

demonstrated in the NSABP B-21 study (24). In this three-arm trial, 1,009 women with pathologically small tumors (≤ 1 cm) and negative axillary nodes were randomized to tamoxifen alone, RT plus placebo, or RT plus tamoxifen following BCS. At 8 years, patients in the RT plus placebo group has a lower incidence of IBTR compared to tamoxifen alone (9% *vs.* 17%), and patients who received RT plus tamoxifen had the lowest incidence of IBTR (2.8%). Notably, a follow-up study in a subset of patients suggested that the local control benefit of adding tamoxifen to RT disappeared after 14 years of follow-up (25).

To more definitively quantify the effect of RT on recurrence and survival, the EBCTCG performed a meta-analysis of over 10,000 patients from 17 randomized trials of RT versus no RT after BCS (26). In 7,287 women with pathologically node-negative disease, RT reduced the 10-year risk of any first recurrence from 31% to 16%, and the 15-year risk of breast cancer death from 21% to 17%. Subgroup analyses in node-negative women revealed that RT approximately halved the recurrence rate across the board, though the absolute risk reduction varied by age, tumor grade, ER status, and tamoxifen use. The authors demonstrated that, on average, one breast cancer death was prevented by year 15 for every four recurrences prevented by year 10, thereby confirming the survival benefit of RT after BCS.

In most of the studies included in the EBCTCG meta-analysis, RT was delivered in 2 Gy fractions to total doses of 50–60 Gy. However, radiobiological models suggest that shorter treatment courses with larger doses per fraction may be just as effective as standard schedules (27), and retrospective clinical data from the United Kingdom (UK) and Canada suggested such schedules yield satisfactory cosmetic and disease outcomes (28-30). These data, coupled with the desire to improve convenience and reduce cost, led to the more formal investigation of alternative fractionation schedules in randomized trials. In 2002, Whelan and colleagues published the results of their trial of 1,234 women with node-negative breast cancer treated with lumpectomy and randomized to either 50.0 Gy in 25 fractions or 42.5 Gy in 16 fractions (31). At a median follow-up of 69 months, there were no differences between the two groups in terms of 5-year local recurrence-free survival (LRFS), DFS, OS, or global cosmetic outcome. The equivalence between the two groups in terms of disease and cosmetic outcomes persisted at 10 years (32).

The UK Standardization of Breast Radiotherapy (START) A and B randomized trials also compared alternative

fractionation schedules to standard fractionation in women with early breast cancer (33,34). The START A trial randomized 2,236 women to either 50.0 Gy in 25 fractions over 5 weeks or 41.6 or 39.0 Gy in 13 fractions of 3.2 or 3.0 Gy over 5 weeks; the START B trial randomized 2,215 women to 50 Gy in 25 fractions over 5 weeks or 40 Gy in 15 fractions over 3 weeks. In both of these trials, 10-year local-regional recurrence (LRR) rates did not significantly differ between randomization arms, and normal tissue effects favored the hypofractionated schedules (35). The Canadian and START randomized trials, along with others (29,36), prompted ASTRO to formulate an evidence-based guideline for the use of hypofractionation (37).

Across all of the randomized trials of WBI, there is considerable variation in the utilization and dose of a tumor bed boost. For example, patients randomized to the breast-conserving therapy (BCT) arm of the NSABP B-06 trial received 50 Gy to the whole breast without a boost (14), while those randomized to the BCT arm of the EORTC 10801 trial received 50 Gy to the whole breast followed by a boost of 25 Gy to the lumpectomy cavity using an iridium-192 implant (18). Among the hypofractionation trials, no boost was used in the Canadian trial (31), while patients were stratified by the pre-planned use of a boost in the START trials (33,34).

Notably, randomized trials have demonstrated that a tumor bed boost improves local control, but not OS, in patients receiving WBI (38,39). In the EORTC boost trial, 5,318 women with early breast cancer were treated with lumpectomy and ALND followed by 50 Gy in 25 fractions to the whole breast, then randomized to no additional RT or a tumor bed boost of 16 Gy in 8 fractions (using electrons, photons, or iridium-192). At 20 years of follow-up, the local recurrence rates were 16% in the no boost group and 12% in the boost group; the absolute risk reduction was largest in patients ≤ 40 years old (36% *vs.* 24%) (40). The 20-year rate of moderate to severe fibrosis was higher in the boost group (30% *vs.* 15%).

As in DCIS, breast cancer investigators have sought to identify a subgroup of patients with invasive disease for whom RT after BCS can be safely omitted. To this end, the Cancer and Leukemia Group B (CALGB) 9343 trial randomized 636 women 70 years or older with T1N0M0 ER-positive breast carcinoma treated with lumpectomy to tamoxifen plus RT or tamoxifen alone (41). At 10 years, 98% of patients in the tamoxifen plus RT group were free from LRR, versus 90% of patients in the tamoxifen only group (42). Time to mastectomy, time to distant metastasis,

and OS did not differ between the groups, though the study was not powered to prove non-inferiority of either arm. A more recent, larger trial (PRIME II) had a similar study design but expanded eligibility criteria to include women age 65 or older (43). The incidence of IBTR at a median follow-up of 5 years was 1.3% in the women randomized to RT and 4.1% in the women randomized to no RT, but the groups did not differ in terms of regional recurrence, distant metastases, or OS. Both of these trials conclude that in older patients treated with adjuvant endocrine therapy, RT provides a statistically significant but clinically modest improvement in local control without affecting survival.

Another potential option in appropriately selected patients is APBI. As discussed in the previous section, selection criteria for APBI vary across professional organizations, and ongoing randomized trials are seeking to better understand which patients are best suited for this treatment strategy. For example, NSABP B-39/RTOG 0413 is a phase III randomized trial of WBI versus APBI in patients with stage 0–II breast cancer and ≤ 3 positive nodes (www.rtog.org). This trial is now closed to accrual and primary outcome results are not yet published.

Summary and recommendations

- (I) BCS plus WBI has equivalent disease-specific outcomes when compared to mastectomy. The addition of WBI to BCS reduces the risk of recurrence and breast cancer death;
- (II) Hypofractionation has become the preferred treatment in nearly all patients who require adjuvant WBI without the addition of a third field to cover regional nodal basins;
- (III) The addition of a tumor bed boost improves local control, and should be routinely offered in young women (<50) or those with high grade disease;
- (IV) Omitting RT can be considered in patients 70 or older with stage I, ER-positive disease if the patient accepts the risk of 10% local failure at 10 years and is willing to take endocrine therapy;
- (V) APBI is an accepted alternative in select patients and continues to be an area of active investigation.

Non-locally advanced, node-positive breast cancer treated with up-front surgery

Patients with non-locally advanced breast cancer with 1–3 pathologically positive nodes after up-front surgery present

a particular challenge when it comes to deciding on the use of adjuvant RT. Surgery for these patients typically includes BCS or mastectomy plus SLNB with or without completion ALND.

When reviewing the literature, it is important to keep in mind that the role of adjuvant RT varies not only by pathologic findings but also by type surgery performed (BCS *vs.* mastectomy, SLNB *vs.* ALND). Here we will first examine the evidence for post-mastectomy RT (PMRT; includes RT to the chest wall and undissected regional lymphatics), and later evidence for regional nodal irradiation (RNI; includes RT to the undissected regional lymphatics), which is applicable to patients treated with either BCS or mastectomy. In patients treated with BCS, RNI is accompanied by RT to the whole breast. In patients treated with mastectomy, RNI is accompanied by RT to the chest wall (essentially PMRT). In general, “undissected regional lymphatics” includes the axillary apex (level III axilla) and supraclavicular fossa, while inclusion of the low axilla and internal mammary nodes varies. This section will discuss the role of adjuvant RT in patients with non-locally advanced, node-positive disease.

Review of the evidence

In the 1980s, the Danish Breast Cancer Cooperative Group (DBCCG) ran two parallel trials evaluating the role of PMRT in pathological stage II and III breast cancer. The first of these trials, DBCCG 82b, randomized 1,708 premenopausal women who had undergone mastectomy and ALND to either eight cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) plus PMRT or nine cycles of CMF alone (44). The second trial, DBCCG 82c, randomized 1,375 postmenopausal women who had undergone mastectomy and ALND to tamoxifen plus PMRT or tamoxifen alone (45). In both studies, patients who received RT had lower LRR and higher OS rates at 18 years (46,47). A smaller study conducted around the same time in British Columbia randomized 318 premenopausal women with pathologically positive nodes after mastectomy and ALND to CMF plus PMRT or CMF alone (48). On 20-year follow-up analysis, the addition of RT was associated decreased LRR and improved OS (49).

In both of the Danish trials as well in the British Columbia trial, the majority of patients enrolled had 1–3 positive nodes (62% in DBCCG 82b, 58% in DBCCG 82c, 58% in British Columbia). However, the nodal burden may have been underestimated as the median number of nodes

removed on ALND was relatively low in all three trials (7 in Danish, 11 in British Columbia). A subsequent re-analysis of the Danish trials looked at patients with 1–3 positive nodes who had at least eight lymph nodes removed, and found that PMRT was still associated with decreased LRR and improved survival (50). In 2014, the EBCTCG published a comprehensive meta-analysis of PMRT using data from 8,135 women in 22 randomized trials, with a focus of those with a complete level I/II axillary dissection (51). The analysis found that for the 1,314 women found to have 1–3 positive nodes on ALND, the addition of RT improved LRR (20% *vs.* 4% at 10 years), overall recurrence (46% *vs.* 34% at 10 years), and breast cancer mortality (50% *vs.* 42% at 20 years).

Though many argue that the results of the previously described studies support the use of PMRT in all node-positive patients, several other studies demonstrate that the local recurrence rate in patients with 1–3 positive nodes treated with mastectomy, adequate ALND, and systemic therapy is approximately 12% at 10 years (52–54), which is lower than the local recurrence rates described in the Danish trials and the EBCTCG meta-analysis. Even so, the addition of PMRT in these studies reduces the 10-year LRR rate by an absolute margin of approximately 10%.

Two recently published trials have further evaluated the role of RNI in primarily N1 patients. In the National Cancer Institute of Canada (NCIC) MA.20 trial, 1,832 women with node-positive or high-risk node-negative breast cancer treated with BCS and SLNB and/or ALND were randomized to WBI plus RNI (including the supraclavicular and internal mammary lymph nodes, and axillary nodes in patients without an adequate dissection), or WBI alone (55). Dissection of levels I and II of the axilla was required in patients with a positive SLNB. Most patients on the trial had 1–3 positive axillary nodes (85%). At 10 years, there was no significant difference in OS between the two groups (83% in WBI plus RNI, 82% in WBI only). However, patients who received RNI had modest but significant improvements in DFS (82% *vs.* 77%), local-regional DFS (95% *vs.* 92%), and distant DFS (86% *vs.* 82%).

The second trial, EORTC 22922/10925, enrolled 4,004 women with stage I–III breast with one of the following: (I) a centrally or medially located tumor, with or without axillary involvement; or (II) an externally located tumor with axillary involvement (56). After treatment with either BCS or mastectomy with SLNB and/or ALND, patients were randomized to RNI (including the supraclavicular and internal mammary nodes) or no

RNI. As in MA.20, all patients who had a positive SLNB were required to have a completion ALND. At 10 years, OS was 82% in the RNI group and 81% in the no RNI group ($P=0.06$). Though the OS difference did not achieve statistical significance, the addition of RNI significantly improved 10-year DFS and distant DFS (72% *vs.* 69% and 78% *vs.* 75%, respectively), and reduced the rates of any first recurrence and death from breast cancer. This trial was limited in that the majority of patients were not planned using a CT simulation, and thus it is likely that target and normal tissue doses were not optimized relative to contemporary standards.

In both the MA.20 and EORTC 22922 trials, completion ALND was required in patients who had a positive SLNB. However, the need for completion ALND in clinically node-negative patients with small-volume axillary disease has in itself been a topic of intense investigation for the last decade. In fact, efforts to optimize management of the axilla began in the 1970s with NSABP B-04 (57). In this trial, clinically node-negative patients were randomly assigned to radical mastectomy (included ALND), total mastectomy with nodal RT, or total mastectomy alone (with ALND reserved for axillary recurrence). At 25 years, there were no differences between the three groups in terms of any survival outcomes. Interestingly, the rate of axillary recurrence in patients who received mastectomy alone was 19%, which was lower than expected given that 39% of patients on the radical mastectomy arm had occult positive nodes. The study was the first to suggest that up-front local-regional treatment of the axilla may not be necessary in all patients, though its applicability is limited in the current era of effective systemic therapy and sentinel lymph node evaluation.

More recently, the American College of Surgeons Oncology Group (ACOSOG) conducted a phase III non-inferiority trial (ACOSOG Z-0011) that randomized 891 clinically T1 or T2, N0 women with 1 or 2 positive lymph nodes at the time of lumpectomy and SLNB to either completion ALND or no further surgery (58). The investigators found that the use of SLNB alone was not inferior to ALND in terms of 5-year OS (approximately 92% for both groups) and 5-year DFS (approximately 83% for both groups). The 5-year rates of local recurrence were low in both groups and not significantly different (1.6% for SLNB alone, 3.1% for axillary dissection). Of note, 27% of patients randomized to completion axillary dissection had additional positive lymph nodes.

The International Breast Cancer Study Group (IBCSG)

also conducted a randomized non-inferiority trial of SLNB alone versus completion ALND (59). In contrast to Z-0011, patients could have BCS or mastectomy, and only patients with micrometastatic foci (≤ 2 mm) of nodal disease were allowed. As in Z-0011, the investigators found that the use of SLNB alone demonstrated non-inferiority compared to ALND in terms of 5-year DFS. The applicability of these results to patients treated with mastectomy and SLNB remains unclear, as these patients comprised only 9% of the study population.

Finally, the EORTC 10981/22023 AMAROS trial compared ALND to axillary RT in clinically node-negative patients with one or more positive nodes on SLNB (60). Axillary RT targeted all three levels of the axilla as well as the medial supraclavicular fossa. The primary outcomes of 5-year axillary recurrence was similar between groups (0.4% after ALND and 1.2% after axillary RT), though the study was underpowered to show non-inferiority due to the low number of events. DFS and OS did not differ between groups. Replacing ALND with axillary radiation reduced the relative risk of upper extremity lymphedema by approximately 50%.

Though the purpose of the above trials was to define the role of axillary dissection, their results muddy the waters with regard to the role of RNI in non-locally advanced node-positive patients. For example, the results from ACOSOG Z-0011 would suggest that women with 1–2 positive sentinel lymph nodes have a low recurrence rate after WBI alone, and therefore RNI is unlikely to be beneficial. However, a recent study by Jagsi and colleagues analyzed the RT records for a subset of 228 patients on Z-0011 and found that approximately half of patients were treated with high tangents (a technique that increases coverage of the low axilla), and 19% of patients were treated with a third RT field, despite this being prohibited by the protocol (61). These findings underscore the fact that the Z-0011 trial results do not apply to patients who do not receive adjuvant RT, or to patients in whom the selected RT technique provides minimal axillary coverage (APBI, prone setup). Considering the proportion of patients who received third field RT, Jagsi *et al.* concluded that adding RNI in select higher-risk patients who meet Z-0011 criteria is reasonable (61).

The decision to recommend RNI in non-locally advanced, node-positive patients has become quite nuanced, and many clinicians rely on nomograms to guide their recommendations. Researchers at MD Anderson developed a nomogram for estimating the likelihood of additional

positive nodes after SLNB based on pathologic findings (62). At our institution, we commonly offer RNI to patients whose estimated risk of additional positive nodes is >25%, a threshold based loosely on the proportion of patients in the ALND arm of Z-0011 who had additional positive lymph nodes not removed on SLNB. Other reasons to consider RNI in these patients are based on retrospective data and include young age, lymphovascular space invasion (LVSI), extracapsular extension, close or positive margins, inadequate axillary dissection, and a ratio of positive to removed lymph nodes of >20% (52-54,63-65).

While most of the research questions in the treatment of N1 patients revolve around RNI, ongoing studies are also evaluating APBI as a possible option for these patients. For example, patients with small tumors and ≤ 3 positive lymph nodes were eligible for enrollment on the NSABP B-39/RTOG 0413 phase III randomized trial of WBI versus APBI (www.rtog.org). Despite the eligibility of node-positive patients, this group comprises a minority on the trial, likely reflecting physician concern about omitting any nodal RT in this group.

Summary and recommendations

- (I) PMRT (and by extension RNI) improves disease-specific outcomes in all node-positive patients treated with up-front surgery;
- (II) In patients with 1–2 positive nodes on SLNB and for whom RT is planned, no further axillary surgery is required, though consideration should be given to intentional coverage of the undissected low axilla. In such patients, adding RNI should be considered if the MDACC nomogram indicates a >25% chance of additional positive nodes, or if the patient has additional high risk features (young age, LVSI, inadequate ALND, etc.);
- (III) In patients who are found to have positive sentinel lymph nodes at the time of mastectomy, the axilla should be addressed either by completion ALND or by axillary radiation. Based on the current evidence, it is not appropriate to observe a patient with positive nodes after mastectomy and SLNB only, though this practice pattern is becoming increasingly common off protocol in the United States;
- (IV) The randomized trials of SLNB only versus ALND included only patients with clinically node-negative disease and are therefore not generalizable to clinically node-positive patients. Clinically node-

positive patients treated with up-front surgery should undergo axillary dissection. The management of clinically node-positive patients treated with up-front chemotherapy is reviewed in the next section;

- (V) The role of APBI in non-locally advanced, node-positive patients is under investigation, and is not recommended outside of a clinical trial.

Locally advanced and non-locally advanced node-positive breast cancer treated with neoadjuvant chemotherapy

For patients with non-locally advanced, clinically node-positive disease, treatment with up-front surgery or up-front chemotherapy are both appropriate options, and decisions regarding adjuvant RT can be made based on surgical findings. For patients with stage III disease or higher, the current standard of care includes a combination of surgery, systemic therapy, and RT. Patients with stage III disease treated with up-front surgery should go on to receive systemic therapy and RT, in accordance with the PMRT trials discussed in the previous section.

However, for all node-positive patients, chemotherapy prior to surgery (neoadjuvant chemotherapy) is becoming the preferred approach, and has long been the standard of care in patients with T4 tumors or advanced lymph node disease (66). Neoadjuvant chemotherapy has several advantages, such as increasing rates of breast preservation (67-69) and providing important prognostic information (70,71). Because most of the available randomized data for adjuvant RT pertain to patients treated with up-front surgery, optimal management of the axilla and regional nodes after neoadjuvant chemotherapy remains controversial. This section will discuss the role of adjuvant RT in patients treated with neoadjuvant chemotherapy.

Review of the evidence

Both BCS and mastectomy are acceptable approaches for management of the primary tumor following neoadjuvant chemotherapy. Management of the regional nodes after neoadjuvant chemotherapy is more controversial. The NSABP B-18 study (a trial of pre-operative *vs.* post-operative chemotherapy) demonstrated that 89% of patients with clinically node-positive disease had clinical response to pre-operative chemotherapy, and 32% had a pathological complete response (pCR) (67). As a result, the indications for adjuvant RT established in the up-front surgical setting

no longer apply, and we must rely on other studies for guidance. Because adjuvant PMRT was not allowed on NSABP B-18 trial or the subsequent NSABP B-27 trial, these studies provides valuable information in terms of recurrence risk without PMRT. In a combined analysis of the two trials, Mamounas and colleagues found that the risk of LRR varied with pathologic response (72). For example, the 10-year cumulative incidence of LRR in patients with a pCR in the breast and nodes after mastectomy was 0%. In contrast, the rate of LRR in patients with residual positive nodes after mastectomy ranged from 17% to 22%, a rate high enough to warrant consideration of adjuvant RT.

A large retrospective analysis from MD Anderson provides insight into the effect of PMRT on outcomes following neoadjuvant chemotherapy (73). In this study, PMRT reduced the 10-year LRR rate versus mastectomy alone (22% with no PMRT to 11% with PMRT) despite the fact that patients referred for adjuvant RT tended to have more advanced disease. In subset analyses, PMRT reduced LRR in patients with T3 or T4 tumors, N2 or N3 disease, ≥ 4 positive lymph nodes, or residual tumors > 2 cm. PMRT also reduced LRR in patients with stage III or IV disease who achieved a pCR (33% with no PMRT to 3% with PMRT). In contrast, there was no observed benefit in patients with stage I or II disease with pCR, or in stage II patients with 1–3 positive nodes after chemotherapy, though patient numbers in these subsets were small. A subsequent analysis of only stage III patients with a pCR corroborated the association between PMRT and reduced 10-year LRR even in patients with no residual disease (33% with no PMRT to 7% with PMRT) (74).

An important ongoing trial (NSABP B-51/RTOG 1304) seeks to further define the role of adjuvant RT in clinically node-positive patient who become node-negative following neoadjuvant chemotherapy (www.rtog.org). In this trial, patients with pathologically confirmed N1 disease at diagnosis are treated with 12 weeks of neoadjuvant chemotherapy followed by surgery (BCS or mastectomy plus SLNB or ALND). Patients with histologic documentation of negative axillary nodes are then randomized to either RNI or no RNI if treated with BCS or PMRT or no PMRT if treated with mastectomy. The primary endpoint is invasive breast cancer recurrence-free interval. This trial recently opened in the United States, with a goal accrual of 1,636 patients over 5 years.

Summary and recommendations

(I) In patients with non-locally advanced, node-positive

disease, response to neoadjuvant chemotherapy should guide adjuvant RT recommendations. At our institution, we commonly offer PMRT/RNI to stage II patients with residual nodal disease, and in select patients with residual breast disease and other high risk features. For clinically node-positive, stage II patients who achieve a pCR, we encourage enrollment on B-51 and consider omission of PMRT/RNI if the patient is not eligible for B-51;

(II) PMRT/RNI should be offered to all patients with T3 or T4 tumors or with clinical stage III disease, irrespective of the response to neoadjuvant chemotherapy.

Inflammatory breast cancer (IBC)

IBC is a unique subgroup of locally advanced breast cancer that requires additional treatment considerations and closely coordinated multi-disciplinary care. In contrast to other types of breast cancer, there are no randomized clinical trials of treatments in these patients, partly owing to the rarity of the disease. The current standard of care for the definitive management of these patients is neoadjuvant chemotherapy, mastectomy (when possible), and PMRT. This section will discuss the role of adjuvant RT in the definitive management of IBC.

Review of the evidence

Even with neoadjuvant chemotherapy, surgery, and PMRT, IBC has a higher risk of local recurrence than non-IBC (75). Several institutional studies have explored the use of dose escalation to combat local recurrence. In a large series from MD Anderson, patients with IBC treated with PMRT to a total dose of 60 Gy were retrospectively compared to those treated with PMRT to 66 Gy to determine the effects of dose escalation on local control (76). Five-year local-regional control for patients who completed treatment was 84%. Higher dose was associated with improved local-regional control in patients who were younger (≤ 45 years), had poor response to chemotherapy, or had close or positive margins. Additional single institution studies from Memorial Sloan Kettering and the University of Pennsylvania report similar rates of local control (87–88%) with more frequent use of bolus in patients receiving 50 Gy (77,78).

Because local-regional disease in IBC can be especially morbid, aggressive local therapy may be justified in patients

with metastatic disease. A recent study reports a 5-year OS of 50% for metastatic patients with a substantial response to chemotherapy who go on to receive surgery and PMRT (79), suggesting that aggressive treatment in these patients should be considered when feasible.

Summary and recommendations

- (I) The curative treatment of IBC requires all three modalities, and the preferred sequence of delivery is neoadjuvant chemotherapy, then mastectomy (with ALND), then PMRT;
- (II) We recommend some form of treatment intensification (by dose, fractionation, or bolus) for all IBC patients. At our institution, we typically dose escalate to 66 Gy in all patients, either in daily or twice daily fractions. Treatment intensification with twice daily fractions is typically reserved for young patients or those with poor response to neoadjuvant chemotherapy. If using daily fractions, we treat to 50 Gy in 25 fractions to the chest wall and draining lymphatics followed by a boost to the chest wall of an additional 16 Gy in 8 fractions. If using twice daily fractions, we treat to 51 Gy in 34 fractions to the chest wall and draining lymphatics followed by a boost to the chest wall of 15 Gy in 10 fractions;
- (III) Aggressive local treatment should be considered in metastatic patients with a marked response to chemotherapy, recognizing that data for this approach is limited.

Conclusions

Radiation plays a vital role in the curative management of all stages of breast cancer by eradicating residual microscopic disease in the breast, chest wall, and regional nodal basins. Careful integration of radiation with systemic therapy and surgery is required to optimize the therapeutic ratio of treatment and minimize patient harm. A multidisciplinary approach is therefore of vital importance in the management of breast cancer, and radiation oncologists should make every effort to promote collaborative treatment planning and implementation with their colleagues in breast surgery and medical oncology.

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Footnote

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References

1. Brennan ME, Turner RM, Ciatto S, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. *Radiology* 2011;260:119-28.
2. Alvarado R, Lari SA, Roses RE, et al. Biology, treatment, and outcome in very young and older women with DCIS. *Ann Surg Oncol* 2012;19:3777-84.
3. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998;16:441-52.
4. 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;12:21-9.
5. 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;31:4054-9.
6. Wärnberg F, Garmo H, Emdin S, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-up in the randomized SweDCIS Trial. *J Clin Oncol* 2014;32:3613-8.
7. 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;2010:162-77.
8. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999;353:1993-2000.
9. Fisher ER, Land SR, Saad RS, et al. Pathologic variables predictive of breast events in patients with ductal carcinoma in situ. *Am J Clin Pathol* 2007;128:86-91.
10. Hughes LL, Wang M, Page DL, et al. Local excision alone

- without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:5319-24.
11. 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;33:3938-44.
 12. 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;33:709-15.
 13. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009;74:987-1001.
 14. 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;347:1233-41.
 15. Arriagada R, Lê MG, Rochard F, et al. 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;14:1558-64.
 16. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr* 1992;(11):19-25.
 17. Poggi MM, Danforth DN, Sciuto LC, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. *Cancer* 2003;98:697-702.
 18. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;92:1143-50.
 19. 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;347:1227-32.
 20. 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;12:997-1003.
 21. Liljegren G, Holmberg L, Bergh J, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999;17:2326-33.
 22. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. *Lancet* 1996;348:708-13.
 23. Holli K, Hietanen P, Saaristo R, et al. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. *J Clin Oncol* 2009;27:927-32.
 24. 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;20:4141-9.
 25. Fisher ER, Costantino JP, Leon ME, et al. Pathobiology of small invasive breast cancers without metastases (T1a/b, N0, M0): National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-21. *Cancer* 2007;110:1929-36.
 26. 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;378:1707-16.
 27. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679-94.
 28. Ash DV, Benson EA, Sainsbury JR, et al. Seven-year follow-up on 334 patients treated by breast conserving surgery and short course radical postoperative radiotherapy: a report of the Yorkshire Breast Cancer Group. *Clin Oncol (R Coll Radiol)* 1995;7:93-6.
 29. Olivetto IA, Weir LM, Kim-Sing C, et al. Late cosmetic results of short fractionation for breast conservation. *Radiother Oncol* 1996;41:7-13.
 30. Shelley W, Brundage M, Hayter C, et al. A shorter fractionation schedule for postlumpectomy breast cancer patients. *Int J Radiat Oncol Biol Phys* 2000;47:1219-28.
 31. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002;94:1143-50.
 32. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513-20.

33. START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371:1098-107.
34. START Trialists' Group, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9:331-41.
35. 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;14:1086-94.
36. Yarnold J, Ashton A, Bliss J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* 2005;75:9-17.
37. 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;81:59-68.
38. 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;15:963-8.
39. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25:3259-65.
40. 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;16:47-56.
41. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971-7.
42. 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;31:2382-7.
43. Kunkler IH, Williams LJ, Jack WJ, et al. 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;16:266-73.
44. 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;337:949-55.
45. 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;353:1641-8.
46. Nielsen HM, Overgaard M, Grau C, et al. Loco-regional recurrence after mastectomy in high-risk breast cancer-risk and prognosis. An analysis of patients from the DBCG 82 b&c randomization trials. *Radiother Oncol* 2006;79:147-55.
47. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, et al. 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;24:2268-75.
48. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med* 1997;337:956-62.
49. Ragaz J, Olivetto 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;97:116-26.
50. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007;82:247-53.
51. 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;383:2127-35.
52. Recht A, Gray R, Davidson NE, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;17:1689-700.
53. Katz A, Strom EA, Buchholz TA, et al. Locoregional

- recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. *J Clin Oncol* 2000;18:2817-27.
54. Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 2004;22:4247-54.
 55. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional Nodal Irradiation in Early-Stage Breast Cancer. *N Engl J Med* 2015;373:307-16.
 56. Poortmans PM, Collette S, Kirkove C, et al. Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer. *N Engl J Med* 2015;373:317-27.
 57. Fisher B, Jeong JH, Anderson S, et al. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002;347:567-75.
 58. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305:569-75.
 59. Galimberti V, Cole BF, Zurrada S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013;14:297-305.
 60. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303-10.
 61. Jagsi R, Chadha M, Moni J, et al. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014;32:3600-6.
 62. Mittendorf EA, Hunt KK, Boughey JC, et al. Incorporation of sentinel lymph node metastasis size into a nomogram predicting nonsentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node. *Ann Surg* 2012;255:109-15.
 63. Woodward WA, Strom EA, Tucker SL, et al. Locoregional recurrence after doxorubicin-based chemotherapy and postmastectomy: Implications for breast cancer patients with early-stage disease and predictors for recurrence after postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2003;57:336-44.
 64. Katz A, Strom EA, Buchholz TA, et al. The influence of pathologic tumor characteristics on locoregional recurrence rates following mastectomy. *Int J Radiat Oncol Biol Phys* 2001;50:735-42.
 65. Wallgren A, Bonetti M, Gelber RD, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J Clin Oncol* 2003;21:1205-13.
 66. Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: a National Cancer Institute conference. *J Clin Oncol* 2008;26:791-7.
 67. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 1997;15:2483-93.
 68. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008;26:778-85.
 69. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001;19:4224-37.
 70. Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg* 1999;230:72-8.
 71. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007;25:4414-22.
 72. 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;30:3960-6.
 73. 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;22:4691-9.
 74. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1004-9.
 75. Wright JL, Takita C, Reis IM, et al. Predictors of

- locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. *Cancer* 2013;119:16-25.
76. Bristol IJ, Woodward WA, Strom EA, et al. Locoregional treatment outcomes after multimodality management of inflammatory breast cancer. *Int J Radiat Oncol Biol Phys* 2008;72:474-84.
77. Damast S, Ho AY, Montgomery L, et al. Locoregional outcomes of inflammatory breast cancer patients treated with standard fractionation radiation and daily skin bolus in the taxane era. *Int J Radiat Oncol Biol Phys* 2010;77:1105-12.
78. Abramowitz MC, Li T, Morrow M, et al. Dermal lymphatic invasion and inflammatory breast cancer are independent predictors of outcome after postmastectomy radiation. *Am J Clin Oncol* 2009;32:30-3.
79. Akay CL, Ueno NT, Chisholm GB, et al. Primary tumor resection as a component of multimodality treatment may improve local control and survival in patients with stage IV inflammatory breast cancer. *Cancer* 2014;120:1319-28.

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