American Radium Society™ Appropriate Use Criteria

POSTMASTECTOMY RADIOTHERAPY

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**Conflict of Interest Disclosure Statement**

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

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**Methodology**

This manuscript is an update to a previously published review study by the American College of Radiology (ACR) Appropriateness Criteria® Panel on “Postmastectomy Radiotherapy”.¹ The reference document focused on the role of postmastectomy radiotherapy (PMRT) in patients diagnosed to have invasive breast cancer and treated with mastectomy with or without reconstruction, and adjuvant or neoadjuvant systemic therapy.

Treatment of patients with locally advanced breast cancer, including large tumors or those involving the skin or chest wall, and breast cancers with extensive lymphadenopathy, is addressed in the ACR Appropriateness Criteria® on “Locally Advanced Breast Cancer”.²
Summary of Literature Review

For this update, a generalized search was first performed for randomized clinical data, systematic reviews and meta-analyses published after the last publication of this AUC in 2009. An analysis of the medical literature from peer-reviewed journals was conducted from 5/4/10 to 11/22/19 using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to search the PubMed database to retrieve a comprehensive set of relevant articles. The search strategy was developed based on National Library of Medicine® Medical Subject Headings (MeSH®) with addition of subject-specific keywords. The bibliographies of full articles were reviewed to exclude studies which were not relevant. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments. A well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures. The expert panel is composed of multidisciplinary radiation, medical, and surgical oncologists as well as additional members with subject-specific expertise.

A literature search based on the highest level of available evidence was conducted for each of the additional topics when higher levels of evidence were not identified. The search phrase methodology used as follows: ("Breast Neoplasms"[All Fields] OR "breast cancer"[ti] OR "breast neoplasms"[ti]) AND ("Mastectomy"[Mesh] OR "mastectomy"[ti]) AND ("radiotherapy"[ti] OR "radiation"[ti])) NOT ("Mastectomy, Segmental"[Mesh] OR "Breast Carcinoma In Situ"[Mesh]) AND ((Randomized Controlled Trial[ptyp] OR Systematic Review[ptyp] OR Meta-Analysis[ptyp]) AND "2010/05/04"[PDat] : "2019/11/22"[PDat] AND English[lang]). Relevant references from the previously published American College of Radiology (ACR) Appropriateness Criteria® Panel on “Postmastectomy Radiotherapy” were retained for the Evidence Table.

Introduction/Background:

Benefit of Postmastectomy Radiation in Reducing Local Regional Recurrence (LRR):

Patients undergoing mastectomy and axillary dissection have clinical and pathologic risks factors for local regional recurrence (LRR) that include patient age, tumor size, tumor grade, presence of lymphovascular invasion (LVI), positive excision margins, involvement of the fascia or skin, number of involved lymph nodes (LNs), and percentage of nodal involvement (or nodal ratio). The most frequent site of LRR is the chest wall. Axillary or supraclavicular recurrences are more common in patients with four or more positive LNs compared to patients with less than four positive LNs. In the setting of modern systemic therapy, PMRT is shown to improve outcomes for breast cancer with poor prognostic risk factors.

Recently, improved understanding of the intrinsic biologic subtypes in breast cancer, including hormone receptor and HER2 status, as well as the molecular genetic profile of the cancer, has
helped define a patient’s risk for relapse. In a retrospective review of a large national database, the benefit of PMRT on preventing LRR was highest for patients with Luminal A subtype and lowest for patients with triple negative disease, and none of the patients who received trastuzumab for HER2-positive disease had LRR. Another retrospective review of 2081 patients enrolled in the Dutch Breast Cancer Cooperative Group 82b/c examined the prognostic and predictive value of the tumor’s intrinsic subtype and gene profile on risk for LRR after mastectomy; they suggested that the assignment of tumors to intrinsic subtypes was unreliable, and gene profiling was better at predicting benefit from PMRT. Combined analysis of premenopausal woman with node positive breast cancer from the British Columbia and Danish Breast Cooperative Group 82b trials showed improvement in LRR with PMRT for the combined data (HR 0.34, 95% CI 0.19 to 0.61) but especially for luminal A tumors (HR 0.12, 95% CI 0.03 to 0.52). An assessment of the 21-gene recurrence score in the mastectomy patients treated without radiation or lumpectomy patients treated with breast radiation in NSABP B14, B20 and B28 studies showed a significant association between the recurrence score (RS) risk group and the risk of local-regional recurrence (LRR), with a higher RS associated with a higher risk of LRR, in both node negative and node positive patients (26,27). An observational cohort from the National Cancer Database (NCDB) and SEER database of women with T1-2N1 ER-positive breast cancer with a known 21-gene RS, undergoing mastectomy with or without radiation, showed a significantly better overall survival in women with a low RS who underwent PMRT, but not in these with intermediate or high RS, suggesting radiation most benefits women at the lower risk of distant metastases. The prognostic value of biologic features, in addition to known histopathology characteristics, is currently being studied in a cooperative clinical trial, MA39 (NCTNCT00005957), which incorporates biomarkers such as the 21-gene recurrence score (Oncotype DX) to risk-stratify patients who may benefit from PMRT [see Variants 5, 6 and 7].

Clinical Topic 1: Role of Postmastectomy Radiation in Stage II Node Positive Disease:

The role of PMRT is well established for patients at high risk of LRR with four or more positive lymph nodes. However, some uncertainty remained as to the role of PMRT in patients with one to three involved LNs.

The EBCTCG meta-analysis of patients with 1-3 positive lymph nodes after mastectomy showed that even in the setting of systemic therapy, significant benefits in LRR and breast cancer mortality were seen with randomization to PMRT. PMRT reduced the risk of LRR by one-third and the risk of breast cancer mortality by one-fifth. An analysis of women with T1-2 LN-positive breast cancer from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program demonstrated 8% improvement in 10-year OS for patients with seven or more positive LNs but was not associated with reduced mortality in patients with one to six positive LNs. A meta-analysis of patients with T1-2 breast cancer with 1-3 lymph nodes showed an absolute LRR
benefit of 6.9% without a benefit in OS.\textsuperscript{34} An analysis of patients with less than 4 nodes positive and T1-2 disease enrolled in the Breast International Group 02-98 trial also found a significant decrease in LRR for patients who received PMRT compared to those who did not (2.5% compared to 6.5%, p = 0.005), but this difference did not translate to a difference in OS.\textsuperscript{33}

Following the results of the ACOSOG Z0011 study,\textsuperscript{35,36} many patients with 1 to 2 positive sentinel lymph nodes do not receive axillary lymph node dissection after mastectomy. Patients in this study received breast conserving surgery for early stage breast cancer with clinically negative axilla. At 10 year follow up, omission of axillary lymph node dissection did not compromise survival. Nearly all patients received radiation therapy and many received nodal radiation.\textsuperscript{37} The OTOASOR trial included patients with mastectomy and clinical T<3cm, N0 breast cancer randomized to completion axillary lymph node dissection (ALND) versus regional nodal irradiation.\textsuperscript{38} Additional positive lymph nodes were found in 38.5% of the patients with ALND, but no difference was seen survival or axillary recurrence. Omission of ALND in the setting of positive sentinel lymph nodes likely necessitates the use of regional lymph node irradiation, although randomized data is not available.

When more than one adverse risk factor, such as young age, premenopausal status, large tumor size, high tumor grade, presence of lymphovascular invasion, positive margin status, high nodal ratio (number of positive LNs/total LNs resected), and high risk intrinsic subtype or 21-gene recurrence score, is present in the setting of nodal involvement, more aggressive locoregional management may be warranted. Additional prospective data evaluating the role of PMRT in intermediate risk patients are expected from an ongoing study BIG 2.04 MRC/EORTC SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy) [see Variants 3 and 10].\textsuperscript{39,40}

\textbf{Clinical Topic 2:}

\textbf{Role of Postmastectomy Radiation in Pathologically Node Negative (pT3N0; positive mastectomy margins):}

Patients with node negative disease are considered low risk for LRR. However, benefits can still be seen in large pooled analyses. A meta-analysis of patients receiving megavoltage radiation after mastectomy with finding of node negative disease showed 83% reduction in LRR rate (p<0.001) without statistically significant changes in OS.\textsuperscript{13} More than 80% of local recurrences occurred in the chest wall. Combinations of risk factors, such as young age (<50), tumor size >2 cm, grade 3 histology or lymphovascular invasion lead to LRR > 15% while the absence of risk factors lead to LRR rate of less than 5%.\textsuperscript{9,41}

The EBCTCG meta-analysis showed conflicting results regarding the use of PMRT in patients with node negative breast cancer.\textsuperscript{11} Patients with axillary dissection and node negative breast cancer had a LRR of only 1.4% and demonstrated a mortality detriment with PMRT. In contrast, patients with axillary sampling (less than 10 lymph nodes excised) had a baseline LRR rate of
16.3% and showed improvements in overall recurrence (RR 0.61, 95% CI 0.47 to 0.80) without improvements in survival. However, this analysis did include data from patients treated with older techniques with several studies omitting treatment of the chest wall.

Triple-negative disease represents a high-risk subgroup that could benefit from PMRT even at early stage. A randomized control examined the benefit of PMRT for patients with triple-negative early stage I-II breast cancer after mastectomy and systemic chemotherapy. At 5-years follow up, recurrence free survival was improved from 74.6% to 88.3% (p=0.02) and OS was improved from 78.7% to 90.4% (p=0.03) with PMRT.

Pathological stage T3N0 disease is a rare clinical presentation, and several conflicting prospective and retrospective studies have been published on this subset of patients. The prospective Danish 82b and Danish 82c study included subset of 135 and 132 patients with stage T3N0 tumors; they observed reductions in LRR in patients receiving PMRT as well as an improvement in 10-year actuarial OS for pre-menopausal patients but not post-menopausal. The NSABP found that for node negative patients with tumors less than 5 cm, the total rates of LRR, including patients with distant failure, was 10% (Taghian, JCO, 2006). In contrast, a SEER database analysis of 635 patients aged ≥ 75 years with T3N0 breast cancer after mastectomy found improved 5-year OS (64.2% vs 44.8%) with receipt of PMRT, but results may have been confounded by comorbidities. An analysis of the NCI SEER database, consisting of 1,777 patients with pT3N0 disease treated with mastectomy, reported that 32% of patients with pT3N0 disease received PMRT. Due to limitations of the SEER database, this study could not report LRR rates, but it did find that PMRT was not a significant predictor of OS or cause-specific survival.

Positive margins after mastectomy can occur after total mastectomy and are more common with skin sparing mastectomies. Retrospective data shows higher risk of LRR for positive and close (≤ 2 mm) margins. This risk may remain elevated after re-excision to negative margins. Higher rates of 5-year LRR was found with positive margins (6.2%) versus uninvolved margins (1.8%, p = 0.013) in the absence of radiation therapy. However, at least one large retrospective study of 2,507 patients did not show a benefit for patients with positive margins after mastectomy. Patients with otherwise low risk disease (age > 50 years, T1 tumors, no LVI and grade 1 or 2) did not have LRR. The benefit of PMRT in the setting of close or positive margin has not been determined.

Given the conflicting prospective and retrospective data, the treatment of patients with triple negative disease, pT3N0 or positive margins with PMRT continues to be individualized, taking into consideration the extent of nodal dissection, the use of systemic therapy, the final pathologic margin status, the presence of lymphovascular invasion, and the intrinsic biologic subtype [see Variants 5 and 6].
Clinical Topic 3
Role of Postmastectomy Radiation Following Neoadjuvant Chemotherapy (NAC):

The role of PMRT may differ in patients who received neoadjuvant chemotherapy (NAC) from that established for patients receiving adjuvant chemotherapy. In the former, the risk of relapse should be considered in context of the known clinical and pathologic factors of disease, and the observed pathologic response to NAC.

A meta-analysis of 24 studies, almost all retrospective, showed local regional failure rates of less than 10% for patients who received neoadjuvant chemotherapy and did not have high risk factors such as T3N1, N2-3 or T4 disease. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) group combined information from over 13,000 patients enrolled in 12 trials of NAC to further understand the interaction between pCR and tumor biology on risk of relapse. Patients who achieved pCR after NAC had improved OS. Eradication of tumor from the breast alone had lower event free survival (HR 0.60, 95% CI 0.55-0.66) and OS (HR 0.51, 95% CI 0.45-0.58) compared to complete eradication of tumor from the breast and nodes (EFS HR 0.44, 95% CI 0.39-0.51) and OS (HR 0.36, 95% CI 0.30-0.44). The biology of the cancer influenced the rate of pCR and also the prognostic value of pCR. More aggressive subtypes had higher rates of pCR ranging from 7.5% for hormone receptor–positive, HER2-negative grade 1 to 2 tumors, to 33.6% for triple-negative tumors, to 50.3% for HER2-positive, hormone receptor–negative tumors that were treated with trastuzumab.

Ongoing trials, including the NSABP B-51/RTOG 1304 and Alliance 011202, will contribute much needed data to the topic of PMRT after NAC [see Variants 9 and 10]. In patients treated with neoadjuvant chemotherapy followed by mastectomy, use of adjuvant radiation is based on the pre-chemotherapy clinical stage and the post-chemotherapy pathologic stage. PMRT is indicated for all patients with residual positive nodes after NAC and should be strongly considered for those with clinical or pathologic nodal disease at diagnosis and pathologic response to NAC (ypN0).

Special Technical Considerations

Treatment techniques:

Several techniques have been described to treat the chest wall after mastectomy, including 3D conformal field-in-field, IMRT, protons and en face electrons. CT simulation is necessary to determine the depth of the supraclavicular fossa, location of undissected lymph nodes, location of the IM vessels, and dose to organs at risk. In addition, CT imaging may influence the photon energy necessary and necessity of a posterior axillary boost. Other treatment strategies including patient positioning and deep inspiration breath hold (DIBH) may be used to reduce the exposure to organs at risk.
Typically, PMRT is planned using 3D conventional tangential fields, but alternative techniques may help spare normal organs at risk. In particular, a simulation of treatment planning showed that 4-field IMRT significantly spared the heart when treating left sided breast cancer compared to tangential fields, tangential IMRT and single arc VMAT. Mean heart dose decreased from 8.7 Gy to 3.5 Gy when using 4-field IMRT compared to tangential fields.

Treatment of the IM nodes presents several challenges. A separate electron field or a combination of low-energy photons and electrons can be used to treat the first three intercostal spaces. Another technique described is the use of partially wide tangential fields with blocking of the heart and inferior lung. Deep tangents may be considered. However, excessive dose to the lung and heart should be avoided. IMRT and rotational arc techniques in some patients will reduce the higher isodoses to heart and lungs while maintaining good coverage of the target volumes, but will also typically result in higher volumes of these organs and the contralateral breast or chest wall receiving low doses. Individualized techniques should be evaluated in the context of each patient’s risk of breast cancer recurrence and co-morbidities.

In a meta-analysis of 75 trials published from 2010 to 2015 with 40,781 patients, direct internal mammary chain field produced increased risk of lung cancer (HR 2.42, 95% CI 1.4 to 4.18) and contralateral breast cancer (HR 1.36, 95% CI 1.11 to 1.67); increased risk of lung cancer was also seen with use of wide tangents (HR 2.21, 95% CI 1.23 to 3.98). Many treatment plans may deliver up to 60% of the prescription dose to the IM nodes without prescribing dose to the IM nodes explicitly.

**Treatment volumes:**

Consultation of breast cancer contouring atlas can improve target and normal structure delineation. Given the variability of target and normal structure delineation for breast cancer, several expert panels have developed breast cancer contouring atlases for RT treatment planning.

It is generally accepted that the entire chest wall and mastectomy scar should be included in clinical treatment volumes. There may be institutional variation regarding the dorsal border of the chest wall target volume. While RTOG recognizes the anterior pleural surface as the dorsal border, ESTRO recommends the anterior surface of the pectoralis major muscle unless there is evidence of invasion. The RADCOMP Consortium trial uses the anterior surface of the ribs as the posterior border. The choice of dorsal border should reflect the tradeoff between increased exposure of heart and lung to radiation versus decreased recurrence posterior to the pectoralis muscle and rib surface. At least one retrospective review showed low levels of recurrence posterior to the surface of the ribs.

There is much more controversy as to which nodal regions to include. For most LN-positive patients, the ipsilateral supraclavicular fossa is usually included in the treatment volume. The inclusion of IM lymph nodes is more variable due to concerns over potential increase in cardiac toxicity and the uncertain additional benefit of nodal irradiation to chest wall RT alone.
A multicenter phase 3 trial (EORTC 22922/10925) examined the value of IM and medial supraclavicular chain irradiation for patients with positive axillary LNs or tumors located centrally or medially. Most patients had early stage tumors, with no nodal involvement (44.4%) or with 1-3 axillary nodes (43.1%). Three-quarters of patients received lumpectomy. At 10 years follow-up, a marginal benefit in overall survival was seen in the group receiving nodal radiation (82.3% vs 80.7%, p = 0.06). Notably, toxicity from nodal irradiation was mostly confined to increased risk of pulmonary fibrosis (4.4% in treated versus 1.7% in controls) and not cardiac events. Disease free survival improved from 69.1% to 72.1% (HR 0.89, 95% CI 0.80 to 1.00). Therefore, the prevention of one local relapse required the treatment of 30 patients.

The MA-20 National Cancer Institute of Canada clinical trial demonstrated an improvement in DFS with the use of regional nodal irradiation in the setting of lumpectomy, including IM LNs, in node-positive or high-risk node-negative patients treated with breast-conserving surgery followed by whole breast RT. In this trial, 85% of patients had 1 to 3 positive lymph nodes and the remainder were at high risk for recurrence. While no improvements in overall survival were seen, disease free survival at nearly 10 years follow up was 82% in the nodal treatment group and 77% in the whole breast only group (HR 0.76, 85% CI 0.61 to 0.94). This equates to the prevention of one relapse for every 20 patients treated. Significant increases in radiation dermatitis (40.1% versus 49.5%) and lymphedema (4.5% versus 8.4%) were seen with treatment of the regional nodes. They reported a very small increase in grade 2 or greater radiation pneumonitis (0.2% versus 1.2%).

In light of the marginal benefits seen with regional nodal irradiation for early stage breast cancer, the benefit of IM nodal radiation alone is difficult to ascertain. A population-based study from the Danish Breast Cancer Cooperative Group trials made use of the natural random allocation of patients based on tumor laterality to IM radiation to determine if IM radiation increased overall survival in patients with early stage node-positive breast cancer. Due to concerns about cardiac toxicity with IM radiation, left sided tumors were not treated with IM radiation from 2003 to 2007 in the study population. In contrast to the EORTC and MA-20 trials, this cohort had a higher proportion of women with positive lymph nodes. Around two-thirds of the patients had 1 to 3 positive nodes and 26% had 4 or more positive nodes. At 8-years, the survival rate was 72.2% (95% CI, 69.2% to 74.9%) with compared to 64.8% (95% CI, 61.8% to 67.7%) without IM nodal radiation. The number needed to treat was 14 patients to prevent one death. Furthermore, cardiac mortality was similar between the two groups. On subgroup analysis, patients with 4 or more lymph nodes, grade 2 or 3 disease or tumor size greater than 5 cm had the largest benefit from IM radiation.

However, a French study randomized 1334 patients after mastectomy to PMRT to the chest wall and medial supraclavicular lymph nodes with or without treatment of the IM nodes. Eligible patients had positive axillary lymph nodes or medial/central tumor location. Treatment of the IM nodes did not result in a significant difference in 10-year OS. Examination of several subgroups, including node positive and receipt of chemotherapy, also did not show improvement with IM
nodal radiation. Controversies over nodal volumes will continue until further randomized evidence is obtained addressing the benefit of nodal radiation for higher risk patients and whether subgroups of patients may safely have omission of IM nodal treatment. A combined analysis of the EORTC, MA-20 and French trial showed a benefit in recurrence and survival with treatment of IM nodes and medial supraclavicular lymph nodes for stages I-III breast cancer. The HR for OS was 0.88 (95% CI 0.78-0.99). Therefore, small improvements in OS may be possible with regional nodal radiation that were not detectable on the individual trials.

Extrapolating from available evidence from the lumpectomy setting, early stage breast cancer without high risk features has a small benefit from nodal irradiation. Patients with high risk breast cancer likely require comprehensive nodal radiation as part of their treatment plan. Alternatively, patients at higher risk for cardiac mortality or secondary lung cancer may have increased risk of toxicity from IM radiation. Decisions on nodal radiation should be tailored to the patient’s net benefit from treatment after consideration of nodal recurrence risk and risk of toxicity from cardiac morbidity and secondary lung cancer [see Variants 1, 2, 3, 4, 9 and 10].

**Dose fractionation:**

The dose delivered to the chest wall is usually 50-50.4 Gy in 1.8-2 Gy daily fractions. Occasionally a 10-16 Gy boost to the mastectomy scar is added, particularly in patients with a positive margin. The dose to the supraclavicular/axillary apical field is usually 45-50.4 Gy in 25-28 fractions.

The original studies for hypofractionation in breast cancer included a limited number of patients treated with mastectomy, but most did not have treatment of regional nodal volumes. The START A and B trials have reported acceptable late tissue effects and tumor control with treatment schedules of 13-15 fractions at 250-320 cGy per fraction. In the British Columbia randomized trial 37.5 Gy was delivered in 16 fractions to the chest wall, while the supraclavicular and axillary fields received 35 Gy in 16 fractions.

Randomized studies of hypofractionated PMRT show lower levels of acute toxicity and similar outcomes, albeit with more limited follow up. A phase III study from China randomizing 820 high-risk patients to conventional (50 Gy in 25 fractions) versus hypofractionated radiation (43.5 Gy in 15 fractions) has reported non-inferiority at 5 years of follow up in respect of LRF and improvements in acute grade 3 skin toxicity. All patients had treatment of the chest wall, level III axilla and supraclavicular fossa. Most patients received treatment to the chest wall using 6 MeV electrons using 2-dimensional treatment planning. Perhaps counter-intuitively, skin toxicity was improved with hypofractionation. Acute grade 3 skin toxicity was 3% in the hypofractionated group and 8% in the conventional fractionated group (p<0.0001). A randomized trial by Van Parijs and colleagues showed similar heart function and pulmonary function between conventional radiation and hypofractionated radiation. Grade 1 skin toxicity was significantly improved with hypofractionation (60% versus 30%). Quality of life was likewise improved for patients with hypofractionated treatment in a randomized trial by Versmessen and colleagues. Shahid and
colleagues randomized 300 patients to 27 Gy in 5 fractions, 35 Gy in 10 fractions and 40 Gy in 15 fractions. Local control and toxicity were similar in all three schedules.

The Alliance for Clinical Trials in Oncology is currently investigating with a phase III study of 880 participants the effect of a hypofractionated regimen of PMRT on patients who have breast reconstruction. A prospective phase II study of hypofractionated radiation to the postmastectomy chest wall and regional lymph nodes followed by a scar boost for a total of 49.95 Gy in 15 fractions found no grade 3 toxicities, but 29% reconstructive complications.

Although interest in hypofractionated treatment for PMRT is growing, additional follow up is necessary to determine the long-term safety and efficacy before generalized use. However, it may be appropriate outside the context of a clinical trial for patients without reconstruction if conventional fractionation is not available or is clinically challenging [see Variants 1 and 2].

**Bolus:**

The most common site of local recurrence after mastectomy is within skin and subcutaneous tissues anterior to the pectoralis muscles, but dose to the skin is often inadequate in modern radiation treatment plans. The application of tissue-equivalent bolus can improve dose to the skin. A survey of radiation oncologists in 2004 revealed that 82% of North American responders reported always using bolus compared to 31% of European responders. Frequency of bolus use was every day in 33% and alternate days in 46% of all responders. Bolus thickness was greater or equal to 1 cm in 48% and < 1 cm in 35%. Only 7% of responders used bolus until skin reaction was achieved, commonly brisk erythema or moist desquamation.

Bolus use does significantly increase the probability of acute dermatological skin toxicity and the probability of treatment interruption. Probability of grade 2 dermatitis increased with Dmax greater than 5311 cGy. At least one non-randomized prospective study investigating daily 2 mm bolus showed adequate skin dose and low rates of grade 3 toxicity. Several comparative retrospective studies show equivalent rates of recurrence with or without bolus. Low rates of recurrence (4%-9%) and low rates of grade 2 acute dermatitis (9-10%) were reported without bolus.

Dosimetric evaluation suggests that adequate dose to the skin can be achieved with application of 1 cm bolus in 15 out of 25 treatment days. Alternatively, 2 mm brass mesh bolus could be applied daily, necessitating only one treatment plan. Brass mesh bolus should not be used with higher energy photon beams (>10 MV) due to the risk of neutron formation. Although no randomized data for the effect of bolus application on local recurrence has been published, a clinical trial of 58 patients in Brazil completed accrual in 2014 (NCT01925651). It randomized patients post-

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1 In the context of the global COVID-19 pandemic, hypofractionation of PMRT has been endorsed as a component of the strategy to conserve hospital resources and minimize patient-staff direct interaction thus may be appropriate in certain circumstances. While further data and evidence will emerge from this experience, long term follow up is still required before hypofractionation of PMRT becomes the standard of care.
Bolus use should be customized to the patient’s skin dose without bolus and the patient’s risk of skin recurrence. As some patients may have acceptable skin dose in their PMRT plan without bolus, skin dose from treatment plans with and without bolus should be evaluated and verified according to institutional protocol. Patients with inflammatory carcinoma, positive anterior skin margins or poor skin dose without bolus may benefit more from more aggressive use of bolus while patients with breast reconstruction or poor skin healing may be at greater risk of toxicity with bolus. Aggressive use of bolus may include 1 cm bolus every other day or ≤0.5 cm daily. Less aggressive bolus may use 0.5 cm bolus every other day or no bolus. Removal of bolus after appearance of grade 2 acute dermatitis may help prevent progression to grade 3 toxicity and prevent treatment interruptions [see Variants 1, 2 and 3].

Clinical Topic 4
Timing of Radiation with Respect to Chemotherapy:

A pooled analysis of 3 randomized trials examined the effect of time interval from surgery to chemotherapy and from surgery to radiation. While delay of chemotherapy initiation greater than 6 weeks resulted in worse survival for hormone receptor negative patients, delay of radiation initiation after surgery did not result in worse outcomes for patients receiving long course chemotherapy. Moreover, delay of radiation after chemotherapy did not affect outcomes. In contrast, a retrospective review of 581 patients receiving neoadjuvant chemotherapy followed by surgery showed a significant benefit in survival for patients receiving post-operative radiation within 8 weeks of surgery. The majority of these patients had locally advanced disease (95% had stage IIB or greater disease) and most received mastectomy (75%). The benefit of early RT was noted for all subgroups of hormone receptor status, HER2 status and pCR. Of note, only 7.4% of the study cohort started radiation within the 8-week interval and the median time was 3.2 months. Therefore, selection bias may have affected the results.

Recent small randomized trials have investigated the safety and efficacy of radiation concurrent with chemotherapy. A small study randomizing 112 patients to standard radiation versus standard radiation with chemotherapy versus hypofractionated radiation with chemotherapy found chemotherapy combined with radiation to be safe and effective.

Chemotherapy and PMRT should not be delivered concurrently outside the context of a clinical trial. The initiation of radiation should be as soon as reasonably possible after chemotherapy. For patients with advanced disease who completed NAC, there may be a benefit to starting radiation within 8 weeks of primary mastectomy.
Clinical Topic 5
Timing of Radiation After Reconstruction:

Reconstruction of the breast before or after radiation can be performed with autologous tissue or implant in one or two stages. An analysis of the SEER database showed no negative impact of breast reconstruction on survival for patients receiving PMRT. Implant-based reconstruction is often done in two stages with initial placement of tissue expander at time of mastectomy followed by exchange for permanent implant. Several studies have shown adverse effects of radiation on both the tissue expander and permanent implant. No randomized evidence exists for PMRT pre-implant exchange versus post-implant exchange. A meta-analysis of 20 studies with PMRT to the tissue expander or permanent implant showed higher rates of reconstructive failure (20% vs 13.4%) with PMRT to the tissue expander, but a trend towards higher rate of capsular contracture with PMRT to the permanent implant (24.5% vs 49.5%). In contrast, another meta-analysis of 8 studies showed decreased risk of capsular contracture with PMRT to tissue-expanders, but no significant differences in reconstructive failure. These analyses are hampered by lack of randomized evidence, heterogeneity of methodology and reporting of outcomes, and small numbers of patients. Patient co-morbidities and radiation techniques and doses were also rarely reported.

The required delay of PMRT during the implant expansion stage for placement of the permanent implant presents another potential complication. This delay can be exacerbated by use of neoadjuvant chemotherapy, which prevents expansion during chemotherapy. As a result, several months pass without active systemic therapy and total treatment time is prolonged.

If exchange of the implant is performed after radiation therapy, rates of reconstructive failure may be reduced by increasing the time interval between completion of RT and implant exchange. However, studies looking at this time interval have had mixed results. One study found a significant decrease in reconstructive failure rate with time interval greater than 6 months between PMRT and implant exchange while another did not see this effect for greater than a 4-month interval. At least one study has shown significantly worse satisfaction with radiation during or after reconstruction compared to radiation delivered before reconstruction.

Use of autologous tissue for reconstruction may result in better cosmetic outcome with decreased risk of reconstructive failure. Patient-reported outcomes for patients receiving autologous tissue reconstruction versus implant-based reconstruction show a slightly increased rate of satisfaction across multiple quality of life domains over time with autologous tissue reconstruction. However, autologous tissue-based reconstruction requires specialized surgical techniques that may not be available in all areas. Moreover, the surgery may be more taxing for patients and may not be feasible for older patients, patients with unfavorable body habitus or patients with competing co-morbidities.

Ultimately, the technique and timing of breast reconstruction in the setting of PMRT should be part of a shared decision-making process between the patient, radiation oncologist and surgical
team. Patients with greater benefit from PMRT may do better with radiation before reconstruction in order to prevent delay of PMRT. Patients with a lower estimated benefit from PMRT may be advised on the possible trade-off between lower rates of reconstructive failure but possible higher rates of capsular contracture for PMRT after exchange of the implant. Autologous tissue-based reconstruction may be an attractive strategy for patients who are good candidates and have access to the specialized surgery technique [see Variants 3, 4 and 10].

Summary of Clinical and Technical Topics

- PMRT is recommended for patients with stage III disease (T3N1, T4N1, and T4N2 primary tumors as well as stage T1-2 disease with 4 or more positive LNs).
- The role of PMRT in patients with stage II node positive disease (T1-2 disease and with one to three positive LNs) is not well supported by the data, particularly for patients who have received contemporary systemic therapy. Individualized recommendations are appropriate in some cases.
- Patients with negative lymph nodes but intermediate risk disease, including stage pT3N0 tumor, positive margins or triple negative disease, may benefit from PMRT in terms of locoregional control, although its impact on survival is unclear.
- The role of PMRT with pCR after NAC is actively being studied. Most patients presenting with clinical stage III disease or having residual disease after mastectomy should receive PMRT.
- Hypofractionated radiation to the chest wall and regional lymph nodes may be feasible, but longer follow up is required before it can be recommended for routine use. Hypofractionated radiation to the reconstructed breast should only be done on study.
- PMRT to the reconstructed breast may increase the risk of failure of the reconstructed flap, capsular contracture and poor cosmetic outcome. Additional studies are needed to determine whether outcomes are improved by radiation post-implant versus pre-implant exchange.
- The benefit of IM irradiation in addition to the chest wall and supraclavicular/axillary apex region is unclear, and long-term results from several trials will be important in defining which patients should receive treatment to the IM LNs. Treatment should be considered for patients at risk of IM involvement, such as those with medial or centrally located tumors and multiple positive axillary LNs.
- Three-dimensional treatment planning is standard of care in breast radiotherapy to minimize dose to the lung and heart, particularly the left ventricle and left-anterior descending artery, in order to assure that improvements in breast-cancer-specific survival are not offset by non-breast-cancer mortality.
**Summary of Recommendations**

**Variant 1:** Case: 50 year-old woman with an anatomic pathologic stage pT1c pN2 cM0 grade invasive ductal cancer, hormone receptor positive and Her2 negative, negative resection margin, including 4 of 15 positive axillary nodes with no extranodal extension (ENE).

The panel recommends post-mastectomy radiation to the entire chest wall and regional nodes, to include undissected axilla levels II and III (with attention to the axillary dissection bed on the planning CT), supraclavicular (SC) and internal mammary nodes (IMNs). Inclusion of the IMN volumes should be weighed against dose to organs at risk, especially the dose to the heart and coronary vessels in left sided patients, and dose coverage of IMNs may be compromised as required to protect the cardiac structures from mean dose > 4-5 Gy, with an ideal mean heart dose of < 2 Gy. The panel recommended that a chest wall boost is not appropriate. Use of chest wall bolus is usually appropriate and should be customized to the patient’s anatomy to provide adequate dose to the scar and chest wall. When used, 0.5 cm of bolus daily or 1 cm of bolus every other day are most common. A dose to the chest wall and nodes of 50 to 50.4 Gy in 25 to 28 fractions to the chest wall and of 45 to 50.4 Gy to the regional nodes is usually appropriate, while chest wall dose of 45-46 Gy in 23 to 25 fractions was rated usually not appropriate, but may prescribed be in selected cases with medical indications. Hypofractionation was rated usually not appropriate for these volumes except on protocol.

**Variant 2:** Case: 50 year-old woman with an anatomic pathologic stage pT3 pN1a cM0 grade 1 invasive lobular cancer, hormone receptor positive and Her2 negative, negative resection margins and 2 out of 15 axillary with ENE, with immediate autologous tissue reconstruction.

The panel recommends postmastectomy radiation to the chest wall and regional nodes, to include undissected axilla levels II and III (with attention to the axillary dissection bed on the planning CT), supraclavicular (SC) and internal mammary nodes (IMNs). Inclusion of the IMN volumes should be weighed against dose to organs at risk, especially the dose to the heart and coronary vessels in left sided patients, and dose coverage of IMNs may be compromised as required to protect the cardiac structures. Chest wall boost was rated not usually appropriate and in a patient with a reconstruction may increase late toxicity. Use of bolus was rated usually not appropriate due to the presence of autologous flap. A dose to the chest wall and nodes of 50 to 50.4 Gy in 25 to 28 fractions to the chest wall and of 45 to 50.4 Gy to the regional nodes is usually appropriate, while chest wall dose of 45-46 Gy in 23 to 25 fractions was rated usually not appropriate, but may prescribed be in selected cases with medical indications. Hypofractionation was rated usually not appropriate for these volumes except on protocol.

**Variant 3:** Case: 54 year-old woman status post mastectomy and sentinel node biopsy with immediate tissue expander placement, with anatomic pathologic stage pT1c pN1a cM0 grade 2 invasive ductal cancer with negative resection margins, hormone receptor positive, Her2 negative, and 2 of 3 sentinel nodes with macrometastases but no ENE.
The panel recommends completion axillary dissection as usually appropriate. The panel recommends postmastectomy radiation as usually appropriate whether without any additional axillary surgery, or with additional axillary surgery even if no additional axillary nodes are positive. The panel does not recommend treating regional nodes only but to treat chest wall and regional nodes, to include the full axilla (levels I-III, unless there is a completion axillary dissection, then undissected axilla is usually appropriate, supraclavicular fossa. Treatment of internal mammary nodes was rated may be appropriate and should be weighed against dose to organs at risk, especially the dose to the heart and coronary vessels in left sided patients, and dose coverage of IMNs may be compromised as required to protect the cardiac structures. Chest wall boost was not recommended and may increase toxicity in a patient with a tissue expander and further reconstruction planned. Use of bolus was rated usually appropriate, but no bolus may be appropriate as well, and should be customized to the patient’s anatomy to provide adequate dose to the scar and chest wall. Timing of radiation before reconstruction was rated most appropriate, or after reconstruction if delay of therapy is less than 3 months, but usually not appropriate of delay on radiation treatment will be more than 3 months.

Variant 4: Case: 40 year-old woman with mastectomy and sentinel node biopsy and immediate tissue expander placement for multifocal grade 3 invasive carcinoma, triple negative, anatomic pathologic stage mpT1c pN1mi cM0, a micrometastasis found on sentinel node final pathology. The panel recommends consideration of completion axillary dissection or post-mastectomy radiation may be appropriate, recognizing that standard of care for patients with minimal nodal involvement in breast conservation patients is not to perform additional surgery. Similarly staged patients with mastectomy and no further indications for PMRT are the subject of ongoing randomized trials. PMRT is more strongly recommend without further surgery because of the constellation of risk factors for local-regional recurrence, including young age, multifocal triple negative high grade histology, and a positive node. When treating, the volumes should include chest wall, full axillary and supraclavicular nodes, but including the IMNs with such minimal axillary disease may be appropriate but not required, and a chest wall boost should not be planned. Timing of radiation should be prior to completion of reconstruction or afterwards only if the delay is less than 3 months.

Variant 5: Case: 50 year-old woman with 5.5 cm grade 3 invasive ductal cancer, negative margins, no LVI and two negative sentinel nodes, anatomic pathologic stage T3N0M0. This variant explores the impact of molecular subtype on the indications for PMRT.

PMRT is most strongly recommended for patients with triple negative and ER/PR negative, Her2 positive disease. PMRT is not recommended for ER/PR positive, Her2 negative cancers, or those whose only risk factor is BRCA mutation. If treating with PMRT, the chest wall should be included, and treatment of the regional nodes may be appropriate, and this may depend in part upon the adequacy of pre-surgical staging and surgical assessment of the nodes.
**Variant 6:** Case: 50 year-old with 3.5 cm invasive ductal cancer status post mastectomy and sentinel node with 1 negative sentinel node and no LVI, but a positive deep chest wall margin.

The panel recommends PMRT to the chest wall regardless of molecular subtype or BRCA status due to the presence of a positive margin. Treatment volumes should include the entire chest wall without regional nodes, followed by a boost to the relevant area of the chest wall to 10 to 16 Gy.

**Variant 7:** Case: 59 year-old woman with 3.5 cm grade 1 invasive ductal cancer, no LVI, status post mastectomy and negative sentinel node biopsy with a close (< 1 mm) resection margin.

The panel recommends no PMRT regardless of molecular subtype or BRCA status for this presentation.

**Variant 8:** Case: 50 year-old woman with clinical stage cT3N1M0 triple negative invasive ductal cancer who received neoadjuvant chemotherapy followed by mastectomy and sentinel node biopsy. Final pathology showed complete pathologic response including two negative sentinel nodes.

The panel recommends consideration of enrolling the patient on an ongoing clinical trial examining the role of PMRT in the setting of neoadjuvant chemotherapy based on response to therapy as the evidence-based standards of care in this setting are under investigation. Off protocol, the panel recommends treating with PMRT to volumes including the chest wall and regional nodes.

**Variant 9:** Case: 50 year-old woman with clinical stage cT3N1M0 upper inner quadrant grade 3 invasive ductal cancer, ER/PR+ Her2-, presenting with three suspicious axillary nodes measuring up to 2.4 cm, treated with neoadjuvant chemotherapy followed by mastectomy and sentinel node biopsy. Final pathology showed residual 3.5 cm disease in the breast and negative margins, and no residual disease in the axillary nodes, stage ypT2N0M0.

The panel strongly recommends PMRT to the chest wall and comprehensive regional nodes including full axilla, supraclavicular and IMN volumes, without a chest wall boost.

**Variant 10:** Case: 50 year-old woman with clinical stage cT2N1M0, grade 3 invasive ductal cancer, triple positive and biopsy proven axillary node, treated with neoadjuvant chemotherapy followed by mastectomy and axillary dissection. Pathology showed no residual cancer in the breast and 2 of 15 axillary nodes.

The panel recommends PMRT to the chest wall and regional nodes, to include the undissected axilla (unless there are potential indication to treat the level 1-2 axilla, such as extensive extranodal extension, bulky nodes, or extranodal tumor deposits present), supraclavicular and internal mammary nodes, with attention to dose to organs at risk, and without a chest wall boost. Radiation should be initiated in less than 3 months from the mastectomy.
Summary of Evidence:

Of the 102 reference articles in the Evidence Table, 21 (22%) are randomized controlled trials or controlled trials, 40 (39%) are observational studies, 15 (15%) are clinical studies, 20 (19%) are reviews including meta-analyses, and 6 are other categories including qualitative, quantitative, atlases and surveys. These references span from 1993 to 2019. The oldest referenced studies include the seminal randomized Danish randomized PMRT trials reported by Overgaard, et al., the ECOG randomized trial from Recht, et al., and a prospective institutional study by Uematsu, et al., which was referenced in part for its reporting of toxicity with and without chest wall bolus.

The Strength of Evidence rates Category 1 for 18 references (17%), Category 2 for 57 references (54%), Category 3 for 28 references (27%) and Category 4 for 2 references (2%). The two Category 4 references include a systematic review of radiation after reconstruction and a review of radiation treatment techniques, for which the underlying data were non-prospective.

There are many high-quality randomized trials and large prospective institutional studies regarding breast cancer treatment. The last version of this AUC included 68 references. Our committee determined prospectively to update the references with more contemporary studies while retiring some of the out of date references. It was our stated intention for this update to expand the topic to include more current clinically relevant information on the use of molecular subtyping and genomic assays in the management of breast cancer, as well as a number of clinical scenarios, including neoadjuvant chemotherapy, reconstruction and node negative disease. We also aimed to expand the description of specific technical considerations in the treatment of patients’ post-mastectomy. As many of these topics have not been studied in a prospective randomized format, we expanded the reference list to include more observational, guidelines and other clinical studies.
References:


22. Albert JM, Gonzalez-Angulo AM, Guray M, et al. Patients with only 1 positive hormone receptor have increased locoregional recurrence compared with patients with estrogen receptor-positive progesterone receptor-positive disease in very early stage breast cancer. *Cancer*. 2011;117(8):1595-1601.


38. Savolt A, Peley G, Polgar C, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III,


Reference 79 was published in update after the literature search date cut-off for this panel. The updated reference is: Poppe MM; Yehia ZA; Baker C; Goyal S; Toppmeyer D; Kirstein L; Chen C; Moore DF; Haffty BG; Khan AJ. 5-year Update of a Multi Institution Prospective Phase II Hypofractionated Post-Mastectomy Radiation Therapy Trial. Int J Radiat Oncol Biol Phys
Clinical Condition: Postmastectomy Radiation

Variant 1: 50-year-old woman, infiltrating ductal carcinoma, status post modified radical mastectomy without reconstruction. 1.5 cm upper outer quadrant (UOQ), grade 1, margins (–), 4/15 LNs (+). No extranodal extension, no lymphovascular invasion (LVI), no metastasis, systemic treatment planned (type undecided). ER/PR (+), HER2 not overexpressed.

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<th>Final Tabulations</th>
<th>Group Median Rating</th>
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**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

**Rating Categories:** U Usually not appropriate; M May be appropriate; A Usually appropriate

**Final Tabulations:** A histogram of the number of panel members who rated the recommendation as noted in the column heading (i.e., 1, 2, 3, etc.)

**Disagree:** The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

**References:** Lists the references associated with the recommendation.

**SQ:** Study Quality (1, 2, 3, or 4) of the references listed

**SOE:** S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

**SOR:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
**Clinical Condition:** Postmastectomy Radiation

**Variant 2:** 50-year-old postmenopausal woman, infiltrating lobular carcinoma, grade 1, ER/PR (+), HER2 (–), status post modified radical mastectomy with autologous tissue reconstruction. Final pathology shows a 6.5 cm UOQ tumor, margins (–), 2/15 LNs (+) with extranodal extension. No LVI, no metastasis, systemic treatment planned.

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**Rating:** A - Usually appropriate; M - May be appropriate; U - Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S - Strong; M - Moderate; L - Limited; EC - Expert consensus; EO - Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

**Rating Categories:** U - Usually not appropriate; M - May be appropriate; A - Usually appropriate

**Final Tabulations:** A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

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**SOE:** S - Strong; M - Moderate; L - Limited; EC - Expert consensus; EO - Expert opinion

**SOR:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 3: 54-year-old postmenopausal woman, status post mastectomy with immediate tissue expander placement for two-phased reconstruction and sentinel lymph node biopsy only with 2/3 LN (+) (macrometastases, 15 mm and 7 mm). Final pathology showed a 1.5 cm central tumor, infiltrating ductal carcinoma, grade 2, ER/PR (+), HER2 (-), margins (–). No extranodal extension. No LVI, no metastasis, systemic treatment planned.

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<td>1 1 3 3 8</td>
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<td>Supraclavicular fossa and Level III axilla RT AND</td>
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<td>2 3 3 8</td>
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<td>M</td>
<td>1 1 1 4 1</td>
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<tr>
<td>Central chest wall boost</td>
<td>M*</td>
<td>1 4 2 1</td>
<td>5*</td>
<td>X</td>
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<td><strong>Chest Wall Bolus</strong></td>
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<td>No bolus OR</td>
<td>M*</td>
<td>1 2 1 1 3</td>
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<tr>
<td>Before completion of reconstruction OR</td>
<td>A</td>
<td>1 2 3 2 8</td>
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<tr>
<td>After completion of reconstruction (assume ≤ 3 month delay of RT) OR</td>
<td>M*</td>
<td>1 2 1 4 2</td>
<td>5*</td>
<td>X</td>
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<tr>
<td>After completion of reconstruction (assume &gt; 3 month delay of RT) OR</td>
<td>U</td>
<td>1 2 4 1</td>
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</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

*Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.*

**Rating Categories:** U Usually not appropriate; M May be appropriate; A Usually appropriate

**Final Tabulations:** A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

**Disagree:** The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

**References:** Lists the references associated with the recommendation.

**SQ:** Study Quality (1, 2, 3, or 4) of the references listed

**SOE:** S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

**SOR:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 4: 40-year-old woman, status post mastectomy and sentinel node biopsy for multifocal invasive breast cancer, no focus greater than 1.0 cm, grade 3. Tissue expander based reconstruction at time of surgery. Sentinel node frozen section was negative, but the permanent section shows a focus of metastasis (<2 mm). Cytotoxic chemotherapy is planned. ER/PR (–), HER2 (-).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
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<td>5*</td>
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<td>1 1</td>
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<td>Omission of chest wall RT AND</td>
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<tr>
<td>Supraclavicular fossa and Level III axilla RT AND</td>
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<td>1 2 3 2</td>
<td>5*</td>
<td>X</td>
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<tr>
<td>Before completion of reconstruction OR</td>
<td>A</td>
<td>1 1 2 3 1</td>
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</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

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Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

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SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 5: 50-year-old woman, grade 3 infiltrating ductal carcinoma, status post mastectomy with sentinel lymph node biopsy, tumor is 5.5 cm UOQ, margins (−), 0/2 LNs (+). No blood vessel invasion or LVI, no metastasis, systemic treatment planned.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
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<tr>
<td>Chest wall RT (if ER/PR/HER2 negative)</td>
<td>M*</td>
<td>1 2 4 1</td>
<td>5*</td>
<td>X</td>
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<tr>
<td>Chest wall RT (if ER/PR positive, HER2 negative)</td>
<td>M*</td>
<td>2 2 1 2</td>
<td>5*</td>
<td>X</td>
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<td></td>
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<tr>
<td>Chest wall RT (if ER/PR negative, HER2 positive)</td>
<td>M*</td>
<td>2 1 2 3</td>
<td>5*</td>
<td>X</td>
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<tr>
<td>Chest wall RT (if BRCA1 or 2 positive)</td>
<td>M*</td>
<td>1 3 1 1 2</td>
<td>5*</td>
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<td>Chest wall RT (depending on genomic analysis)</td>
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<td>4 1 2 1</td>
<td>5*</td>
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<tr>
<td>Treatment Volumes (if no further surgery)</td>
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<tr>
<td>Chest wall RT alone OR</td>
<td>A</td>
<td>2 3 3 7</td>
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<tr>
<td>Chest wall RT and regional lymph nodes</td>
<td>M*</td>
<td>4 2 2 2</td>
<td>5*</td>
<td>X</td>
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</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usuall not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

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SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 6: 50-year-old woman, with infiltrating ductal carcinoma, status post mastectomy with sentinel node excision, 3.5 cm UOQ, positive deep margins (tumor at ink, no fascia), 0/1 LNs (+). No LVI, no metastasis, systemic treatment planned (type undecided).

<table>
<thead>
<tr>
<th>Procedure</th>
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<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<td>Principles of Treatment</td>
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<tr>
<td>Chest wall RT (if ER/PR/HER2 negative)</td>
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<tr>
<td>Chest wall RT (if ER/PR positive, HER2 negative)</td>
<td>M*</td>
<td>2 1 2 3 5*</td>
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<td>Chest wall RT (if ER/PR negative, HER2 positive)</td>
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<td>2 2 4 7.5</td>
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<tr>
<td>Chest wall RT (depending on genomic analysis)</td>
<td>M*</td>
<td>2 1 1 3 5*</td>
<td>X</td>
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<tr>
<td>Treatment Volumes (if treating chest wall)</td>
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<tr>
<td>Chest wall RT alone OR</td>
<td>A</td>
<td>1</td>
<td>3 4 7.5</td>
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<tr>
<td>Chest wall RT and regional lymph nodes</td>
<td>M*</td>
<td>5 1 2</td>
<td>5*</td>
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<td>1 4 2 1 7</td>
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**Rating:**
- **A:** Usually appropriate
- **M:** May be appropriate
- **U:** Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:**
- **S:** Strong
- **M:** Moderate
- **L:** Limited
- **EC:** Expert consensus
- **EO:** Expert opinion

**Strength of Recommendation:**
- **↑:** Strong Recommendation
- **↓:** Weak Recommendation
- **-** Not strong, not weak

---

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

**Rating Categories:**
- **U:** Usually not appropriate
- **M:** May be appropriate
- **A:** Usually appropriate

**Final Tabulations:**
A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

**Disagree:**
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**References:**
Lists the references associated with the recommendation.

**SQ:**
Study Quality (1, 2, 3, or 4) of the references listed

**SOE:**
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- **M:** Moderate
- **L:** Limited
- **EC:** Expert Consensus
- **EO:** Expert opinion

**SOR:**
- **↑:** Strong Recommendation
- **↓:** Weak Recommendation
- **-** Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 7: 50-year-old woman, with infiltrating ductal carcinoma, status post mastectomy with sentinel node excision, 3.5 cm UQ, grade 1, close margin (< 1 mm), 0/1 LNs (+). No blood vessel invasion or LVI, no metastasis, systemic treatment planned.

<table>
<thead>
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<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
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<td>Principles of Treatment</td>
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<tr>
<td>Chest wall RT (if ER/PR/HER2 negative)</td>
<td>M*</td>
<td>3 4 2 1</td>
<td>5*</td>
<td>X</td>
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<tr>
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<td>1 6 3</td>
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<td>Chest wall RT (if ER/PR negative, HER2 positive)</td>
<td>M*</td>
<td>1 3 4 2</td>
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<tr>
<td>Chest wall RT (if BRCA1 or 2 positive)</td>
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<td>1 5 4</td>
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<td>1 4 4 1</td>
<td>5*</td>
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Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
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Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate
Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)
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SQ: Study Quality (1, 2, 3, or 4) of the references listed
SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion
SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 8: 50-year-old postmenopausal woman with infiltrating ductal carcinoma, with clinical stage III (cT3N1) infiltrating ductal carcinoma, ER/PR (--), HER2 (--). The patient received neoadjuvant chemotherapy followed by mastectomy and sentinel lymph node biopsy. Final pathology demonstrates no residual tumor in the breast and 0/2 SLN (ypT0N0). Margins (--), no LVI.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
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<tbody>
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<td>A</td>
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<tr>
<td>Treatment Volumes (if treating chest wall)</td>
<td>M*</td>
<td>2 3 4</td>
<td>5*</td>
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<tr>
<td>Chest wall RT alone OR</td>
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<tr>
<td>Chest wall RT and regional lymph nodes</td>
<td>A</td>
<td>4 2 2</td>
<td>7.5</td>
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Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

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References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 9: 50-year-old postmenopausal woman with clinical stage III (cT3N1) infiltrating ductal carcinoma, upper inner quadrant (UIQ), ER/PR (+), HER2 (−). Original tumor was grade 1 in the UIQ with 3 suspected lymph nodes measuring 1.2, 1.5 and 2.4 cm. The patient received neoadjuvant chemotherapy followed by mastectomy and sentinel lymph node biopsy. Final pathology demonstrates 3.5 cm residual tumor in the breast and 0/2 SLN (ypT2N0). Margins (−), no LVI.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<td>Treatment Volumes (if treating chest wall)</td>
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<tr>
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<tr>
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<td>6</td>
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</table>

Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, ... etc.)

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References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical Condition: Postmastectomy Radiation

Variant 10: 50-year-old postmenopausal woman with clinical stage IIB (T2N1) infiltrating ductal carcinoma, grade 3, ER/PR (+), HER2 (+). Prechemotherapy FNA of axillary LN was positive. Treated with neoadjuvant chemotherapy followed by mastectomy and lymph node dissection. Final pathology demonstrates no residual tumor in the breast and 2/15 LN. Margins (−), no LVI. Patient plans on reconstruction at later date.

<table>
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<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SQ</th>
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<td>Radiation to chest wall and regional lymph nodes OR</td>
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<td>Supraclavicular fossa AND</td>
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<td>Internal mammary nodes AND</td>
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<td>1 2 1 2 1 1</td>
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<td>Before completion of reconstruction OR</td>
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<td>After completion of reconstruction (assume ≤ 3 month delay of RT)</td>
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<td>2 1 1 1 1 1</td>
<td>5* X</td>
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