

American College of Radiology ACR Appropriateness Criteria®

POSTMASTECTOMY RADIOTHERAPY

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Summary of Literature Review

This summary focuses on the role of postoperative radiation therapy in patients treated with modified radical mastectomy for invasive breast cancer, particularly in patients receiving systemic therapy. Patients treated with mastectomy for T4, pN3, or clinically node-positive disease is addressed in the ACR Appropriateness Criteria® for “[Locally Advanced Breast Cancer](#)”. Neither radical mastectomy nor simple mastectomy without axillary dissection is in widespread use in the United States; hence the results of studies conducted on such patients will not be reviewed here. (These have been summarized elsewhere [1-5]).

Local-Regional Failure Rates in Unirradiated Patients

In series with median lengths of follow-up of 5 years or longer, local-regional failure occurs at the first site of failure in approximately 15%-20% of node-negative [6-10] and 25%-40% of node-positive patients [6,11-15] with early-stage breast cancer who do not receive systemic therapy. Tumor size [16-23], the number of positive lymph nodes [16,19-21,24-29], lymphovascular space invasion [17,22,23,25,27,30], tumor grade [18,19,22,23,27,29], and the distance of tumor from the pectoralis fascia [18,23,31,32] or involvement of the fascia and skin [33] can influence the likelihood of such recurrences.

Several recent reports confirm the interaction of tumor size, tumor grade, lymphovascular space invasion, surgical margin status, skin involvement, number of involved lymph nodes, number of lymph nodes sampled, and patient age as compounding factors that determine the risk

of local-regional recurrence [17,18,20-23,25,30,33]. Long term local-regional failure rates in patients with locally advanced tumors may be 40% or higher [34].

The chest wall is the site at greatest risk for local-regional recurrence [20,33,35]. The risk of regional nodal recurrence varies with the size of the primary tumor, whether axillary nodes are involved, the number of nodes sampled, the number involved, and by the type of axillary dissection used [18,20,21,29,36,37]. The impact of sentinel node biopsy on local-regional recurrences remains uncertain and will be established with the results from ongoing clinical trials addressing this aspect of treatment outcome. With standard axillary procedures, axillary recurrences are rare following removal of level I and II nodes, when nodes are negative or there are only one to three positive nodes. Nodal relapse in undissected level III lymph nodes and supraclavicular fossa is the second most common type of regional failure. However, such failures are more common in patients with four or more positive nodes [18,20,21,33,38].

The presence of extracapsular nodal extension was associated with a higher risk of distant failure [18,39-43] in some series, with no difference noted in local-regional recurrence. Huang et al reported an association of extracapsular extension with an increased risk of local-regional failure by multivariate analysis [33]. Garg et al [44] reported that extracapsular extension was associated with a 29% risk of local-regional recurrence vs 9% if absent (P=.0834). Clinical recurrences in internal mammary lymph nodes are rare [35].

The impact of chemotherapy on local-regional failure rates has varied among randomized trials involving patients with positive nodes. Some have shown substantial proportional reductions in such failure rates, one-third to one-half lower than the incidence in the control arms [9,12,14,15], but others have shown little to no reduction [10,13,45]. Tamoxifen has been shown to improve local-regional recurrence rates when used for treatment of estrogen receptor (ER)-positive disease [11,44].

Randomized Studies of Postmastectomy Irradiation and Risk of Local-Regional Recurrence

Postmastectomy irradiation reduces the risk of local-regional recurrence (LRR) as documented by innumerable trials over the last several decades. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [46] included 78 prospective randomized trials investigating the value of postsurgical irradiation. The 5-year local recurrence risk was 6% with postmastectomy irradiation and 23% without, providing a risk reduction of 74%. The addition of postmastectomy irradiation provided similar proportional reductions in

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local recurrence in all patients regardless of age or tumor characteristics, and in all the major trials of irradiation vs no irradiation (recent or older, with or without the use of systemic therapy). Large absolute reductions in local recurrence were seen only if the control risk was large.

Many of the trials included in the EBCTCG analysis, however, did not irradiate the area at highest risk of LRR, namely the chest wall, and doses varied widely. A meta-analysis by GebSKI et al [47] identified randomized trials with appropriate tissue coverage (chest wall, axilla, and supraclavicular fossa) treated to a biologically effective dose (BED) of 40-60 Gy (defined as Category 1 trials). For these 26 trials, an 80% reduction in local-regional failure was identified, a result better than that identified in trials not meeting Category 1 criteria.

Randomized Studies of Postmastectomy Irradiation and Benefit for Local Recurrence, Disease-Free Survival, and Overall Survival

Three large prospective randomized trials have reported outcomes analysis for postmastectomy irradiation for premenopausal [41,48] and postmenopausal [41] women. In premenopausal patients, Danish Trial 82b found a statistically significant improvement in rates of local recurrence (32% vs 9%), disease-free survival (34% vs 48%) and overall survival (45% vs 54%) in favor of chest wall and regional lymphatic irradiation plus cyclophosphamide, methotrexate, 5-fluorouracil (CMF) chemotherapy compared with CMF alone [48]. This study included stage II and III patients and had a median follow-up of 10 years. Most of these patients had node-positive disease, but node-negative patients with tumors >5 cm, and/or skin or pectoralis fascia involvement were also eligible. Multivariate analysis confirmed that irradiation after mastectomy was a statistically significant factor in improving disease-free and overall survival rates. This finding was consistent regardless of tumor size, number of positive lymph nodes, or tumor histologic grade.

The Vancouver Trial [49] also examined outcomes for node-positive premenopausal patients randomized to CMF alone vs CMF plus local-regional irradiation. Updated results at 20 years demonstrate statistically significant improvements with PMR for event-free survival, survival free of local failure, breast-cancer-free survival, and overall survival. These results are similar to the findings reported by Danish Trial 82b. This analysis was stratified by number of nodes positive, and no difference in risk reduction by PMR was identified between patients with one to three positive lymph nodes (LNs) and those with four or more positive LNs.

The value of postmastectomy radiation in node-positive postmenopausal patients was prospectively evaluated in Danish Trial 82c [41]. The study design included randomization to tamoxifen for one year only vs tamoxifen plus chest wall and regional lymphatic irradiation, after mastectomy. Ten-year analysis showed improvement in local recurrence rates (35% vs 8%, $P<0.001$), disease-free survival rate (24% vs 36%,

$P<0.001$) and overall survival rate (36% vs 45%, $P=.03$) in favor of patients receiving irradiation. The differences were all statistically significant. The authors found that the outcome seen with irradiation and tamoxifen was similar to the outcome seen in the patient populations within the trial who were treated with CMF and tamoxifen postmastectomy without local regional irradiation. The analysis was also carried out with stratification by the number of positive lymph nodes; all disease outcome measures were still statistically significantly improved with irradiation.

An updated publication [50] from the Danish 82b and 82c [41,48] trials showed continued benefit for postmastectomy irradiation at a median follow-up time of potentially 18 years. Irradiation was found to change disease recurrence patterns in these patient populations. The 18-year probability of any breast cancer event was 73% without RT and 59% with RT ($P<0.001$, RR 0.68, 95% CI 0.63 to 0.75). The 18-year probability of LRR, with or without distant metastases (DM), was 49% without RT and 14% with RT ($P<0.001$, RR 0.23, 95% CI 0.19 to 0.27). The 18-year probability of DM subsequent to LRR was 35% with no RT and 6% with RT ($P<0.001$, 95% CI 0.11 to 0.20). The 18-year probability of any DM was 64% without RT and 53% with RT ($P<0.001$, RR 0.78, CI 0.71 to 0.86).

To further clarify the value of postmastectomy irradiation in premenopausal and postmenopausal women, a subset analysis was completed to evaluate LRR rates and survival in relationship to the number of positive nodes when patients had at least eight or more lymph nodes removed [50]. The survival benefit after postmastectomy RT was substantial and similar for patients with one to three and four or more positive lymph nodes. The overall 15-year survival rates were 39% with RT and 29% without ($P=0.015$); for the four or more node-positive patients the 15-year overall survival rates were 21% with RT and 12% without ($P=0.03$), and for one to three node positive patients, 57% with RT and 48% without ($P=0.03$).

The 15-year loco-regional failure rates for four or more positive nodes were 10% with RT and 51% without ($P<0.001$), and for one to three positive nodes they were 4% with RT and 27% without ($P<0.001$). The survival benefit was not strictly associated with the risk of LRR which was pronounced in patients with four positive nodes.

These three trials have provided specific data to assist in patient selection, and they appear to warrant consideration for chest wall and regional lymphatic irradiation in node-positive premenopausal patients and in postmenopausal node-positive patients receiving tamoxifen therapy only. Importantly, both trials demonstrate overall survival (OS) improvement rates with PMR that were appreciable only with long-term follow-up.

Three meta-analyses of postmastectomy irradiation have reported its overall survival benefit in relationship to the prevention of LRR. An EBCTCG meta-analysis of 78

randomized clinical trials, completed by 1995, evaluated the benefit of irradiation on local control and breast cancer mortality [46]. The benefit on local control has been previously discussed. The addition of RT was found to eliminate one breast cancer death for every four local recurrences that are prevented. The analysis also found that the addition of irradiation increased the risk of contralateral breast cancer (1.18, $P=0.02$) and increased the risk of nonbreast cancer related deaths (1.12, $P=0.001$). Most nonbreast cancer deaths were attributed to cardiac causes and to a lesser extent to lung cancer. Both of these results were seen at 5 years and continued to be evident at the 15-year analysis. As a result, the ECBCTG did not identify an OS benefit with PMR despite the decrease in breast cancer deaths. It did find that avoidance of local recurrence resulted in a significant reduction of breast cancer mortality at 15 years, regardless of patient age or tumor characteristics or, extent of local synergy and in all major trials of RT vs no RT, recent or older, with or without systemic therapy [46]. The second study was an analysis of data on women with T1-2 node-positive breast cancer from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [51]. This analysis found that postmastectomy irradiation was not associated with an excess mortality at a median follow-up of 8.1 years (HR 0.96). Case control analysis confirmed postmastectomy irradiation was associated with a 15%-20% relative reduction in mortality for patients with seven or more positive lymph nodes. Postmastectomy irradiation was not associated with reduced mortality in patients with one to six positive lymph nodes.

The effect of postmastectomy irradiation on long-term mortality from heart disease and lung cancer in the United States was also evaluated in a meta-analysis study using SEER data [52]. Among patients who did not receive RT, tumor laterality was of no relevance to subsequent mortality. The cardiac mortality ratio for left vs right tumor laterality has improved with radiation treatment after 1992. Cardiac mortality ratios for follow-up in less than 10 years: 1973-1982: 1.2; 1983-1992: 1.04; 1993-2001: 0.96; for 10-14-year follow-up, 1973-1982: 1.4, 1983-1992: 1.27; for 15 or more years, 1973-1982: 1.58. The overall trend is for $p < 0.03$. Lung cancer mortality, for either ipsilateral or contralateral disease, the mortality ratio for 1973-1982 is 1.17 at less than 10 years, 2.0 for 10-14 years and 2.71 for 15 or more years. There are few data for any analysis beyond 20 years.

A second SEER study specifically evaluated cardiac mortality from ischemic heart disease [53] with respect to left-sided vs right-sided cancers for all patients receiving radiation. The data confirm that after 1979 the hazard ratio from ischemic heart disease decreased 6% annually.

GebSKI et al [47] performed a meta-analysis of 36 randomized trials for which the only difference between the two treatment arms was the addition of PMR. The process included analysis of the adequacy of radiation dose and anatomic coverage for the chest wall and regional lymphatic areas. For those studies in which dose

and field design were considered biologically and anatomically adequate (Category 1), the odds of local recurrence were reduced by 80%. For studies in which the tissue coverage or dose was considered inadequate, reductions of local recurrence were lower: 70% and 64%, respectively. Unlike the EBCTCG meta-analysis, analysis of the Category 1 data demonstrates an overall survival benefit for PMR at 5 years with HR=0.87, and at 10 years with HR=0.78. This demonstrates that maximum benefit and minimum toxicity are achieved through appropriate treatment dose and field design.

Retrospective studies have shown that local-regional failure rates in patients with locally advanced breast cancer are 10% or lower following irradiation [54-56]. Two randomized trials have been performed to evaluate whether postoperative radiation therapy improves disease-free or overall survival rates for patients with stage III operable cancers [57,58]. One of these trials was very small and is not discussed further. The other one showed no difference in disease-free or overall survival rates between irradiated and unirradiated patients at 5 years, but substantial methodologic flaws confound the interpretation of these results (eg, high rate of unevaluable patients, incomplete reporting of the study population) [57].

Few studies have examined the possible value of nodal irradiation, separate from that of chest-wall irradiation. The earliest randomized trial attempting to examine this issue was The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-01 trial (started in 1961), which showed no difference in outcome whether patients received postmastectomy irradiation to the axillary apical, supraclavicular, and internal mammary nodes or not [59]. However, this study suffered from a high proportion of unevaluable patients, as well as using inadequate radiotherapy doses by today's standards. Trials conducted by groups in Milan and Villejuif, France, attempting to examine this problem accrued very small numbers of patients [60-62]. In a randomized trial performed from 1985-1993 at the National Cancer Institute Hospital in Tokyo, 150 patients with biopsy-proven internal mammary node involvement were randomized to radical resection of the internal mammary node chain and supraclavicular nodes, irradiation of the supraclavicular and internal mammary nodes, or no further surgery or irradiation of this area [63]. All patients received six courses of CMF. The 5-year disease-free survival rates were statistically the same in the three arms (57%, 53%, and 51%), although the risk of supraclavicular and/or internal mammary recurrence was lowest in the irradiated group (32%, 0%, and 16% in the three arms, respectively). Thus, because of the small numbers of patients, limited follow-up, and the other flaws noted, none of these trials has definitively settled this issue. In early 1996 the European Organization for Research and Treatment of Cancer (EORTC) began a trial (protocol 22922/10925) examining the value of internal mammary and medial supraclavicular chain irradiation for patients with positive axillary nodes *or* central or medial tumors

treated with either breast-conserving surgery or mastectomy. The results of this trial are still pending.

Patients occasionally present with pathological stage T3N0 disease. In one recently reported series, pathological stage T3N0 disease represented only 0.9% of breast cancer cases seen [64]. Based on very limited retrospective data, as well as data from one prospective trial, local-regional relapse remains a common site of failure in pathologic stage T3N0 disease [64,65]. A retrospective series by Helinto et al [65] reported local-regional relapse in three of five (60%) patients treated by mastectomy without postoperative irradiation, compared with only three of 33 patients (9%) treated with postoperative irradiation ($P=.0003$). Similarly, in a prospective trial by Klefstrom et al [66] local-regional relapse developed in five of 13 pathological T3N0 patients not randomized to postoperative irradiation compared with none of 27 patients treated with postoperative irradiation ($P=.002$). Failure in the chest wall along the surgical scar is clearly the most common site of relapse with this presentation, followed by supraclavicular failures, and rarely, internal mammary or axillary failures. These results support consideration of treatment to the chest wall in patients with pathologic stage T3N0 breast carcinoma. The value of postmastectomy irradiation for CS T3N0 patients in the neoadjuvant setting has been previously discussed [44].

The routine use of postmastectomy radiation for patients with T3N0 disease has more recently been challenged. In a retrospective analysis by Floyd et al [67] of 70 patients with T3N0 disease, the 5-year rate of local-regional failure without radiation was only 7.6%. However, those patients with lymphovascular space invasion were at significantly higher risk of local-regional failure. In an analysis of 330 T3N0 patients selected from various NSABP studies, Taghian et al [68] reported a total of 28 local-regional failures, resulting in a 10-year isolated local-regional failure rate of 7.1%. Based on these retrospective analyses, the authors challenge the routine use of postmastectomy radiation in patients with pathologic T3N0 disease. Given the limited data available, treatment of T3N0 patients will likely continue to be highly individualized.

Postmastectomy Irradiation following Neoadjuvant Therapy

The introduction of neoadjuvant chemotherapy has enabled patients who are marginal candidates for breast conservation to have breast-conserving surgery if there is good tumor response. Neoadjuvant tumor response also serves as a clinical marker for the success of the systemic treatment program. NSABP B-18 [69] found no differences in DFS or OS when systemic therapy was given in the neoadjuvant or adjuvant setting.

The parameters suggesting the need for postmastectomy irradiation may be different with neoadjuvant therapies compared to adjuvant therapies. The M.D. Anderson Cancer Center has reported a comparison of pathologic features associated with postmastectomy local-regional

recurrence in breast cancer patients not receiving radiation therapy who were treated with neoadjuvant vs adjuvant chemotherapy [38]. The analysis was made from pooled findings of prospective trials involving clinical stage (CS) I-IIIb disease. Patients received doxorubicin-based therapy. Rates of postmastectomy LRR for any pathologic tumor size were higher for patients treated with neoadjuvant chemotherapy (T 0-2 cm, 18% neo vs 8% adj. $P=.011$; T 2.1-5.0 cm, 36% neo vs 15% adj. $P=.001$; and T 5.1 cm or greater 46% vs 28% $P=.028$). The number of involved nodes was also a significant determinant of LRR regardless of the chemotherapy sequence with surgery (greater than four nodes, 53% neo vs 23% adj. $P=.001$). With a T2N2-3+ node group, the LRR was 30% with neo vs 15% adj. $P=.016$. Patients with CS III disease were recommended to receive postmastectomy irradiation regardless of the pathologic tumor and nodal response to neoadjuvant therapy. Huang et al [33] reported a CS II-IV disease, evaluating pathologic predictors of LRR for patients treated with neoadjuvant chemotherapy and postmastectomy irradiation. All patients received doxorubicin-based chemotherapy; standard axillary dissections were performed, with a median of 15 nodes taken. Irradiation was delivered to the chest wall, supraclavicular (SC), and internal mammary (IM) areas, with inclusion of the axilla if insufficient numbers of axillary nodes were sampled. The 5- and 10-year actuarial recurrence rates were 9% and 11%, respectively. Multivariate analysis confirmed significant risk factors for LRR were skin/nipple involvement, SC nodal involvement, no tamoxifen use, extracapsular lymph node extension and ER negative disease. The 10-year rate of LRR with zero or one factor was 4%; with two factors it was 8%, and with three or more factors it was 28%. Patients with multiples of these pathologic factors were considered candidates for additional treatment programs that might further reduce the risk of LRR. In a report from a retrospective series, clinical and pathologic features associated with LRR for patients with CS I or CS IIB disease treated with neoadjuvant chemotherapy without irradiation were associated with CS T3N0 disease ($P=.0057$), four or more positive lymph nodes ($P=.001$), age 40 years or less at diagnosis ($P=.0001$), and no use of tamoxifen with ER positive disease ($P=.0067$) [44].

Postmastectomy Irradiation for DCIS

There is little data available to describe benefit of postmastectomy irradiation in the setting of DCIS. The question most commonly arises with report of close or positive surgical margin status. Rashtigan and Iganej [70] reported that postmastectomy irradiation may be of benefit for patients with very close (less than 3 mm) or positive margins, particularly in the setting of high grade disease. Local recurrences in patients with greater than 3 mm margins were rare.

Their report was made from a retrospective chart review with a median follow up of 49 months. Six of 81 patients (7.4%) had loco-regional recurrences. Chest wall recurrences were noted in 4 patients with the remaining

two patients having axillary recurrences. The recurrence rates in patients with close, very close or positive surgical margins were 2%, 11% and 33% respectively. Patients with high grade lesions had an 11% loco-regional recurrence rate, whereas low to intermediate grade lesions had a 3% recurrence rate. In the subgroup of patients with very close or positive surgical margins who had high grade disease, 24% recurrence rate was observed [70]. In a review of 10 cases of patients with DCIS treated with mastectomy who sustained postmastectomy chest wall relapses, Kim et al [71] noted common features amongst the chest wall relapse cases were young patient age, multiquadrant disease and the presence of residual normal breast tissue. Outcome following salvage radiation for the chest wall recurrences was excellent, with 9 out of the 10 patients alive without evidence of disease. Based on these results and a review of the literature, the authors acknowledge the need for highly individualized decision making and make no firm recommendation regarding indications for post mastectomy irradiation for DCIS.

Treatment Volumes, Techniques, and Doses

No randomized studies focus on the optimal technical parameters of postmastectomy radiation therapy. Hence, the following discussion is based on retrospective data from series of patients treated after both breast-conserving surgery and mastectomy. Because normalization conventions and prescription points differ from institution to institution and there is no consensus on which to use, all doses given are approximate.

The meta-analysis previously described that assessed the association between postmastectomy irradiation for early breast cancer [47] and overall survival also examined the adequacy of field design and dose schedule with respect to LRR and overall survival. Surgery was mastectomy (NOS), and systemic/endocrine therapies were not detailed. Irradiation was evaluated by category, with category I being optimal irradiation dose and tissue coverage, II being inadequate or excessive irradiation, and III being incomplete tissue coverage. The addition of adjuvant irradiation with an optimal biological equivalent dose (BED 40-60 Gy) and target volume (chest wall, axilla, and supraclavicular fossa with or without internal mammary nodes) was associated with a statistically significant improved overall survival rate. At 10-year analysis, irradiated Category I patients had a 6.4% absolute increase in survival rate ($P=.001$). Category II patients did not have a significant difference in overall survival rates.

There are few data on optimal field borders or field arrangements, particularly for nodal irradiation. A detailed discussion of technique is beyond the scope of this effort, especially with regard to such controversial topics as the use of posterior or en-face axillary boosts and the choice of prescription points and dosimetry conventions. However, the panel discussed in depth the issue of when to treat a full axillary field and when to treat a supraclavicular field for patients with four or more positive axillary nodes.

With current widespread treatment techniques and field-border placements, the lower portion of the axilla (level I and part or all of level II) is ordinarily included in the same fields as those used to treat the chest wall. The so-called supraclavicular field (ie, lateral border at the coracoid process) usually includes the level III nodes in most patients, as well as the true supraclavicular nodes more medially. Clinically, this field design may not cover the full infraclavicular fossa/chest wall area, and the physician must be aware of this when choosing “supraclavicular” nodal field design. The “full axillary field” (also called a “supraclavicular/axillary field”) traditionally extends the lateral border of the supraclavicular field/anterior axillary fold to split the humeral head, thus including more soft tissue laterally.

As noted above, the risk of nodal recurrence is low in patients with one to three positive nodes following a level I-II or complete axillary dissection. Patients with four or more involved nodes have been irradiated in most series, but the results have not usually been subdivided by treatment techniques. However, in one series of patients treated with complete (levels I, II, and III) dissection who had 10 or more positive nodes, there was no difference in axillary failure rates, whether a supraclavicular field or a full axillary field was treated [72]. The risk of arm edema is substantially increased by giving full axillary irradiation to patients who have had a complete axillary dissection, but not when patients have undergone a more limited dissection [73-77]. In contrast, the risk of arm edema was only 3% in a recent series of 82 node-positive patients (who had either a level I or II or a complete dissection) treated with a supraclavicular field; none suffered a brachial plexopathy [42].

In the postmastectomy situation the risk of skin recurrence is usually considered to be substantial; hence, the use of bolus to increase the skin dose is common. Whether it is necessary to apply bolus every day or less frequently is uncertain. In a series from the Joint Center for Radiation Therapy that included predominantly patients with clinical stage I-IIIa disease, there was no difference in the frequency of chest-wall failure among patients treated with some bolus (4%) or no bolus (5%) [37]. However, most of these patients were treated on a 4 MV linear accelerator, which (like cobalt-60 teletherapy) delivers a fairly high skin and subcutaneous dose even when bolus is not used. For patients with locally advanced disease (stage IIIB), achieving a high skin and subcutaneous dose may be more important. In a series of patients with inflammatory breast cancer treated postoperatively with cobalt-60 or electron beams at the M.D. Anderson Cancer Center, chest-wall failure was more frequent in those who did not achieve a brisk erythema or moist desquamation (41%, or 7/17) than in patients who did (15%, or 3/20) [55]. In a recent report from Halle, Germany, patients with earlier-stage tumors were treated with electrons following mastectomy and a higher rate of local failure was found in patients who developed mild or moderate erythema during radiotherapy (7%, or 5/72) compared to patients who developed severe

erythema (0 of 58) [78]. However, it is possible that the degree of skin reaction may reflect individual variations in normal-tissue sensitivity to irradiation, which in turn may be a surrogate for tumor sensitivity, rather than being a guide to optimal treatment techniques.

Treatment can also be given with electron beams alone or with mixed photon-electron beams. In a technique developed at the M.D. Anderson Cancer Center, several large fields are matched to one another and irradiated with 7- or 9-MeV electrons [79,80]. Techniques using electron arcs or rotational motions have also been described [81,82]. The advantages and disadvantages of using these modalities have not been rigorously compared, however.

Different centers throughout the world employ very different regimens of total dose and fractionation schedules. Most institutions in the United States treat the chest wall to total doses of approximately 50 Gy in 1.8-2 Gy daily fractions, given five times weekly. However, the M.D. Anderson Cancer Center has used 2.5 Gy fractions to give a dose of 50 Gy in 4 weeks (prescribed to the d^{\max} of the electron beam being used) [54]. Institutions in Europe and Canada have often used even shorter schedules. Canadian/UK trials have reported acceptable late tissue effects and tumor controls with treatment schedules of 13-16 fractions at 250-300 cGy per fraction [83-86]. No excess cardiac mortality has been reported from the British Columbia Cancer Agency database when treatment was analyzed by dose schedules of 2 Gy vs greater than 2 Gy, by left vs right sided cases and by age less than 60 or greater than 60 years of age [87]. Additional studies to evaluate the factorization sensitivity of breast cancer will be reported with results of the United Kingdom Standardization of Radiotherapy (UK-START) trial A. START Trial A of 2,236 patients are randomized to receive 41.6 Gy in 13 fractions of 3.2 Gy and 39.0 Gy in 13 fractions of 3 Gy over 5 weeks. START Trial B will evaluate 2,215 patients treated to 40 Gy in 15 fractions over 3 weeks vs. 50 Gy in 5 weeks [88].

There are no data about whether or in what circumstances giving a boost dose to the mastectomy scar is of value in reducing the risk of local failure compared with treating the entire chest wall uniformly. Furthermore, if a boost is given, no data are available as to an appropriate dose.

Doses of 45-50 Gy appear adequate to eradicate clinically undetectable tumor in lymph nodes in the great majority of cases [36,54]. Higher doses are needed to control grossly involved nodes, although there is no clear evidence for a dose-response curve above 50 Gy [36,89]. Doses above 50 Gy are associated with increased risks of complications, however [36,90].

The optimum sequencing of chemotherapy and radiation therapy following modified radical mastectomy is not known. In one randomized series, radiotherapy given after the completion of 15 or 30 weeks of chemotherapy still very substantially reduced the local-regional failure rate, compared with unirradiated patients [91].

Conclusions

There is clear evidence from large randomized studies and meta-analyses that giving radiation therapy following modified radical mastectomy in high risk patients not only reduces local-regional failure rates but also yields clinically relevant improvements in disease-free and overall survival rates, even when adjuvant systemic therapy is also given. However, as stated in the ACR position paper on postmastectomy radiation therapy [3], questions remain in generalizing from these results because of differences in surgical techniques, radiotherapy techniques, and treatment volumes, as well as differing systemic treatments.

Management Guidelines

Postmastectomy radiotherapy is indicated in patients with T3N1 and T4N1&2 primary tumors as well as T1-2 disease with 4 or more positive nodes. We acknowledge that some controversy remains regarding the benefit of PMR for patients with T1-2N1 disease (ie, one to three positive LNs), and the importance of the consultation process to review the risks and benefits of this therapy cannot be overemphasized. Chest-wall and regional lymphatic radiation therapy for premenopausal node-positive patients or node-positive postmenopausal women receiving tamoxifen therapy only is worthy of consideration, given the potential survival benefit. A radiation oncologist should be consulted for node-positive patients treated with mastectomy to help them assess the risk and benefits of postmastectomy radiotherapy. All postmastectomy patients with primary tumors larger than 5 cm with involved axillary nodes, or locally advanced (T4, N2) tumors should be irradiated. Patients with invasive tumor at the deep resection margin (including patients with negative axillary nodes) should also undergo radiotherapy.

Other treatment issues also need further attention if postmastectomy radiotherapy is to be used with maximum effectiveness and minimum toxicity. These include the interactions of doxorubicin or taxanes with radiotherapy, particularly when administered in high doses [92-94], the timing of chemotherapy and radiotherapy with regard to each other, and the best way to give radiotherapy to patients undergoing reconstruction surgery. Studies [94-96] suggest that concurrent paclitaxel and irradiation are safe.

The chest wall should be treated in all irradiated patients. At simulation the radiation oncologist should check that the radiologic field borders to adequately ensure coverage of the clinical target volume, including scars. The panel's preferred total dose is approximately 50 Gy in 1.8-2 Gy daily fractions, five times weekly. Bolus should be applied to the entire chest wall in patients treated with 6 MV or higher energy photons. Use of a mastectomy scar electron boost is reasonable, and application of boost is based on risk assessment for residual microscopic disease.

Axillary radiotherapy should not be given after removal of level I or II nodes when the nodes are negative. For patients with one to three positive nodes, treatment of the

supraclavicular fossa and axilla is optional. Patients with four or more positive nodes, or those with tumors larger than 5 cm, should be treated to the supraclavicular field. The panel did not strongly recommend treatment of the level I axilla after level I/II dissection when four or more lymph nodes are positive. Treatment of the axilla should be considered whenever there is a question of extensive nodal involvement, as defined by numbers of lymph nodes involved, size (bulk) of nodal disease, or extent of soft-tissue involvement in the axilla, or if there is limited dissection. The panel considered routine doses of 45-50.4 Gy reasonable. Treatment of the internal mammary chain remains controversial. The panel generally supports use of internal mammary treatment for patients having positive axillary nodes with medial or centrally located tumors.

Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- Evidence table under review

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition:**Postmastectomy Radiotherapy****Variant 1:**

50 years of age, infiltrating ductal carcinoma, S/P modified radical mastectomy, 1.5 cm UOQ, margins (-), 4/15 LNs (+). No BVI or LVI, no metastasis, systemic treatment planned (type undecided). ER/PR, Her2, and menopause status will not alter treatment options.

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	9	
Supraclavicular fossa/level III axilla RT	9	
Supraclavicular fossa and level I-III axilla RT	3	
Internal mammary node RT	7	
Central chest wall boost	8	Boost may be appropriate, as indicated by risk of residual microscopic disease relative to the radiation dose achieved with comprehensive chest wall irradiation.
Chest Wall RT (Doses)		
50-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Supraclavicular Fossa/Axillary RT (Doses)		
45-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
IMN Chain RT (Doses)		
50 Gy in 25 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Chest Wall Boost RT (Doses)		
10-16 Gy in 5-8 fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 2:**

50 years of age, grade 3 infiltrating ductal carcinoma, S/P modified radical mastectomy, tumor is 3.5 cm UOQ, margins (-), 0/15 LNs (+). No BVI or LVI, no metastasis, systemic treatment planned (type undecided). ER/PR, Her2, and menopause status will not alter treatment options.

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	1	
Supraclavicular fossa/level III axilla RT	1	
Supraclavicular fossa and level I-III axilla RT	1	
Internal mammary node RT	1	
Central chest wall boost	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3:

50 years of age, postmenopausal woman with infiltrating ductal carcinoma, S/P modified radical mastectomy, 6.5 cm UOQ, margins (-), 0/15 LNs (+), ER/PR (+), Her2 (-). No BVI or LVI, no metastasis, systemic treatment planned (type undecided).

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	7	Recommendation to treat is individualized and based on patient age, tumor grade, margin status and +/- LVI.
Supraclavicular fossa/level III axilla RT	5	
Supraclavicular fossa and level I-III axilla RT	1	
Internal mammary node RT	5	There may be circumstances where nodal radiation is appropriate, depending on optimal chest wall coverage relative to the primary tumor position.
Central chest wall boost	7	Boost may be appropriate, as indicated by risk of residual microscopic disease relative to the radiation dose achieved with comprehensive chest wall irradiation.
Chest Wall RT (Doses)		
50-50.4Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Supraclavicular Fossa/Axillary RT (Doses)		
45-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
IMN Chain RT (Doses)		
50 Gy in 25 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Chest Wall Boost RT (Doses)		
10-16 Gy in 5-8 fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 4:**

54 years of age, postmenopausal woman, infiltrating ductal carcinoma, S/P modified radical mastectomy, 1.5 cm UOQ, margins (-), 2/15 LNs (+), ER/PR (+), Her2 (-). No BVI or LVI, no metastasis, systemic treatment planned (type undecided).

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	7	
Supraclavicular fossa/level III axilla RT	7	
Supraclavicular fossa and level I-III axilla RT	3	
Internal mammary node RT	7	
Central chest wall boost	7	Boost may be appropriate, as indicated by risk of residual microscopic disease relative to the radiation dose achieved with comprehensive chest wall irradiation.
Chest Wall RT (Doses)		
50-50.4Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Supraclavicular Fossa/Axillary RT (Doses)		
45-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
IMN Chain RT (Doses)		
50 Gy in 25 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Chest Wall Boost RT (Doses)		
10-16 Gy in 5-8 fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 5:**

50 years of age, postmenopausal woman, infiltrating ductal carcinoma, S/P modified radical mastectomy, 6.5 cm UOQ, margins (-), 2/15 LNs (+), ER/PR (+), Her2 (-). No BVI or LVI, no metastasis, systemic treatment planned (type undecided).

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	9	
Supraclavicular fossa/level III axilla RT	9	
Supraclavicular fossa and level I-III axilla RT	3	
Internal mammary node RT	8	
Central chest wall boost	8	Boost may be appropriate, as indicated by risk of residual microscopic disease relative to the radiation dose achieved with comprehensive chest wall irradiation.
Chest Wall RT (Doses)		
50-50.4Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Supraclavicular Fossa/Axillary RT (Doses)		
45-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
IMN Chain RT (Doses)		
50 Gy in 25 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Chest Wall Boost RT (Doses)		
10-16 Gy in 5-8 fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 6:**

40 years of age, premenopausal woman with infiltrating ductal carcinoma, S/P modified radical mastectomy, 3.5 cm UOQ, positive deep margins (tumor at ink), 0/15 LNs (+). No BVI or LVI, no metastasis, systemic treatment planned (type undecided).

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	9	
Supraclavicular fossa/level III axilla RT	2	
Supraclavicular fossa and level I-III axilla RT	1	
Internal mammary node RT	2	
Central chest wall boost	9	
Chest Wall RT (Doses)		
50-50.4Gy in 25-28 fractions	9	
37.5 Gy in 16fractions	6	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 7:**

50 years of age, infiltrating ductal carcinoma, S/P modified radical mastectomy, with immediate reconstruction, no BVI or LVI, no metastasis, systemic treatment planned (type undecided), 3.5 cm left UOQ, margins (-), 4/15 LNs (+), post level I-II dissection. ER, PR, Her2 and menopausal status will not alter treatment recommendations.

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	9	
Supraclavicular fossa/level III axilla RT	9	
Supraclavicular fossa and level I-III axilla RT	3	
Internal mammary node RT	7	
Central chest wall boost	8	Boost may be appropriate, as indicated by risk of residual microscopic disease relative to the radiation dose achieved with comprehensive chest wall irradiation.
Chest Wall RT (Doses)		
50-50.4Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Supraclavicular Fossa/Axillary RT (Doses)		
45-50.4 Gy in 25-28 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
IMN Chain RT (Doses)		
50 Gy in 25 fractions	9	
37.5 Gy in 16 fractions	6	In selected cases may be appropriate.
Chest Wall Boost RT (Doses)		
10-16 Gy in 5-8 fractions	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition:**Postmastectomy Radiotherapy****Variant 8:**

45 years of age, with diffuse suspicious calcifications, positive for DCIS, S/P simple mastectomy, no invasive carcinoma, but diffuse high-grade comedo DCIS with a positive deep margin (tumor at ink). Sentinel node at the time of mastectomy was negative.

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	No consensus	Chest wall irradiation may be indicated, depending on tumor grade, histology and the patient's age.
Supraclavicular fossa/level III axilla RT	1	
Supraclavicular fossa and level I-III axilla RT	1	
Internal mammary node RT	1	
Central chest wall boost	No consensus	Boost is considered appropriate if a decision to treat is made.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 9:

40 years of age, S/P mastectomy and sentinel node for multifocal invasive breast cancer, no focus greater than 1.0 cm. Sentinel node frozen section was negative, but the permanent section shows a focus of metastasis (<2 mm). Completion level I/II axillary dissection demonstrates no further tumor in nine lymph nodes. Cytotoxic chemotherapy is planned. ER/PR (-), IHC only (+).

Treatment	Rating	Comments
Principles of Treatment (Volumes)		
Chest wall RT	1	
Supraclavicular fossa/level III axilla RT	1	
Supraclavicular fossa and level I-III axilla RT	1	
Internal mammary node RT	1	
Central chest wall boost	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		