Treatment Guidelines and Techniques in Delivery of Postmastectomy Radiotherapy in Management of Operable Breast Cancer

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Radiation therapy has been shown to statistically significantly reduce the risk of locoregional recurrence in high-risk patients with operable breast cancer following mastectomy and systemic therapy. Recent trials have also demonstrated a significant survival benefit following radiotherapy in high-risk patients. Therefore, it is important to identify the patients who could potentially derive that survival benefit and to not offer treatment to those patients who are not at increased risk for failure. Established risk factors that predict for increased rates of locoregional recurrence include axillary lymph node involvement and T3 (or T4) disease. While treatment-related factors, such as the extent of the axillary dissection and extent of lymph nodal positivity, also undoubtedly affect locoregional recurrence, additional studies are needed to define the magnitude of their risk. Locoregional patterns of failure have identified the chest wall and supraclavicular/infracavicular regions to be the most common sites of locoregional failure following mastectomy, which justifies treatment to these regions. While long-term complications are uncommon following locoregional radiotherapy, careful treatment planning is critical to minimize cardiac (and pulmonary) toxicity. [J Natl Cancer Inst Monogr 2001;30:117–24]

INTRODUCTION

Virtually every retrospective and prospective study examining the effect of radiotherapy (RT) following mastectomy has demonstrated a statistically significant reduction in the risk of locoregional recurrence by the addition of postmastectomy RT (PMRT) (1–15). In the recent update by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) of the overview of 40 randomized trials, a highly statistically significant two-thirds reduction in locoregional recurrence was observed following RT (two-sided P<0.001) (16).

With the significant benefit of RT on locoregional control (LRC), attention is now focused on the effect optimal LRC has on survival. The EBCTCG overview demonstrated a statistically significant reduction in breast cancer deaths for patients randomly assigned to receive RT, with an absolute difference of 4.8% (two-sided P = .001); overall survival was of borderline statistical significance in favor of RT, with 20-year survival rates of 37.1% with RT versus 35.9% among control subjects (two-sided P = .06) (16). A statistically significant survival advantage was seen with the use of PMRT following chemotherapy and mastectomy in two randomized trials from Denmark and British Columbia (12,14), and a second Danish trial (15) found a statistically significant survival benefit with RT and adjuvant tamoxifen. Specifically, a 9% absolute survival benefit at 10 years was demonstrated in the Danish premenopausal trial (82b) for patients randomly assigned to receive RT following mastectomy and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), compared with CMF alone (P<0.001) (14). An identical survival benefit was observed following RT and CMF after 15 years in the smaller British Columbia trial (P = .02) (12). In the Danish Breast Cancer Cooperative Group (DBCCG) postmenopausal trial of mastectomy and tamoxifen (82c) (15), a 9% absolute survival benefit was seen at 10 years for women randomly assigned to receive RT (P = .03). In a meta-analysis by Whelan et al. (17) of RT trials following mastectomy and systemic therapy, a statistically significant reduction in mortality was observed with RT, with an odds ratio of 0.83 (P = .004). Although this analysis was strongly influenced by the positive results of the large premenopausal and postmenopausal Danish trials, it also included the results of 16 other trials published between 1967 and 1999. Thus, these data demonstrate a systemic benefit of postmastectomy RT in high-risk breast cancer patients and emphasize the importance of defining the patients who could potentially derive that survival benefit. This article will review existing selection criteria for postmastectomy RT and will discuss technical aspects and treatment guidelines.

RISK FACTORS FOR LOCOREGIONAL RECURRENCE

Involvement of the axillary lymph nodes is a powerful predictor for locoregional recurrence following mastectomy and chemotherapy in both retrospective and prospective series, with increasing rates of locoregional failure (LRF) associated with increasing lymph node involvement (18–21). In an analysis of four randomized trials conducted by the Eastern Cooperative Oncology Group (ECOG) using adjuvant methotrexate-based regimens, the risk of LRF with or without distant failure was 12.9% in patients with one to three positive lymph nodes and 28.7% for patients with four or more lymph nodes positive at 10 years (19). A series by Stefanik et al. (20), which also studied patients treated with methotrexate-based therapy, demonstrated 5-year rates of actuarial LRF of 9% with one to three positive lymph nodes, compared with 36% with four or more positive lymph nodes. Similar results were recently reported from The University of Texas M. D. Anderson Cancer Center, Houston, with doxorubicin-based therapy, where 10-year actuarial rates of isolated LRF and total LRF were 10% and 14%, respectively, for one to three positive lymph nodes; 21% and 25%, respectively, for four to nine positive lymph nodes; and 22% and 34%, respectively, for 10 or more positive lymph nodes (21).

Although many trials have randomly assigned women to RT following chemotherapy and mastectomy, only a few have reported LRF results by the number of positive axillary lymph...
nodes (Table 1). In general, the incidence of LRF in the absence of RT in most U.S. series has been 5%–15% in patients with one to three positive lymph nodes and 20%–50% in patients with four or more positive lymph nodes at 10 years. As shown in Table 1, the rates of LRF in the British Columbia and Danish trials (12,14,15) exceed these estimates and have caused some to question the extent of the surgical resection in these trials. The median number of axillary lymph nodes dissected was seven in the Danish trials, resulting in increased rates of axillary failure without RT (i.e., 13% axillary failure as first failure in surgical controls versus 2% following RT) (22). The limited axillary surgery may not have adequately identified those patients with one to three positive lymph nodes from those with four or more positive lymph nodes, thus reporting rates of failure usually seen with four or more positive lymph nodes in patients with one to three involved lymph nodes following inadequate dissection (23). These limitations in the data should be considered when incorporating the information learned in the Danish trials into practice guidelines for patients with one to three involved axillary lymph nodes.

Tumor size also appears to be an independent risk factor for LRF following mastectomy, although data are limited in the lymph node-negative population. In the randomized trial by Klefstrom et al. (24) in stage III disease, patients with T3N0 breast cancer treated with RT with or without vincristine, doxorubicin, cyclophosphamide, and levamisole had a 7% risk of LRF as a component of first failure compared with a 38% risk without RT. In the series by Katz et al. (21), the 10-year actuarial isolated rate of LRF with T3 disease and negative lymph nodes was 29%, compared with 6%–11% with smaller lymph node-negative lesions; only seven patients, however, had T3N0 disease in this series. In a larger retrospective series of 101 patients with T3N0 disease (median tumor size of 6 cm), 15% of the patients developed LRF as a component of first failure compared with a 7.8-year follow-up (25). Many series (14,15,19,21,26) have reported the risk of LRF using combinations of tumor size and lymph node involvement. In the ECOG analysis by Recht et al. (19), the risk of LRF in the group with one to three positive lymph nodes increased from 12% to 31% for patients with T1/2 versus T3 lesions and from 20% to 45% in the group with four to seven positive lymph nodes at 10 years. Thus, data from both lymph node-negative and lymph node-positive disease demonstrate increased risk of LRF with T3 disease.

Rates of LRF for other tumor- and treatment-related factors, including estrogen receptor status, tumor grade, S-phase, lymphatic invasion, p53 accumulation, multicentricity, and margin status, have been reported (13,26–32). Conflicting results and limited data have prevented clear assessment of risk, and more studies are needed to establish a consensus. Two additional factors, the presence of extracapsular extension (ECE) and the number of lymph nodes examined, have been more extensively studied and warrant further comment. Reports (33–35) have demonstrated increased rates of LRF and distant failure in patients with microscopic ECE. However, ECE is correlated with increased risk of axillary lymph node involvement (35–37). Donegan et al. (35) reported the presence of ECE in 39% of cases with one to three positive lymph nodes, 78% with four to seven positive lymph nodes, and 92% with eight or more positive lymph nodes. A patterns-of-failure study by Mignano et al. (34) found the chest wall to be the most common site of LRF in patients with ECE, with 16% of patients having a chest wall recurrence and no failures at the axilla or other regional sites. Thus, ECE does not appear to predict for a statistically significantly increased risk of axillary recurrence, and correlation with increasing lymph node involvement may account for chest wall risk.

The number of positive axillary lymph nodes and the number of lymph nodes examined appear to affect the cumulative incidence of the sites of LRF (19). Specifically, in patients with one to three positive lymph nodes, a statistically significantly greater number of axillary failures was observed in the ECOG data when only two to five lymph nodes were examined, compared with when six to 10 and 11 or more lymph nodes were dissected ($P = .0009$). This compared with a statistically significantly greater risk of supraclavicular failure, and not axillary failure, in patients with four or more positive lymph nodes and four to five lymph nodes examined versus six to 10 and 11 or more lymph nodes removed ($P = .02$). Therefore, the extent of axillary resection in conjunction with the number of positive axillary nodes appears to affect the patterns of LRF and should be considered when reporting LRF results.

In summary, accepted risk factors for locoregional recurrence following mastectomy for operable breast cancer include four or more positive axillary lymph nodes and T3 tumor size. ECE does not appear to be an independent predictor of LRF when extent of lymph node positivity is considered. There is no consensus in patterns of recurrence for other tumor-related factors. Further studies are needed. The extent of dissection and the extent of lymph nodal positivity appear to affect patterns of regional failure and should be considered in future studies of locoregional recurrence.

### Impact of Local Control on Survival

As discussed previously, optimal locoregional control with RT has resulted in statistically significant gains in survival. While it is reasonable to assume that patients at high risk for LRF would be the patients most likely to derive a survival benefit, some trials suggest that it is patients at lower risk for LRF who derive the greatest survival benefit. It has been postulated that it is patients with the least systemic burden who can be

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Table 1. Risk of locoregional recurrence with and without radiotherapy (RT) by number of positive axillary lymph nodes

<table>
<thead>
<tr>
<th>Trial, No. of positive lymph nodes</th>
<th>Dana-Farber Cancer Institute (9)</th>
<th>BDCG 82b (14)</th>
<th>SECCSG (30)</th>
<th>BDCG 82c (15)</th>
<th>British Columbia (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Systemic therapy</td>
<td>Locoregional failure</td>
<td>Follow-up, y</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No RT</td>
<td>RT</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>83</td>
<td>CMF</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>CA</td>
<td>20</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>1–3</td>
<td>1061</td>
<td>CMF</td>
<td>30</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>510</td>
<td>CMF</td>
<td>42</td>
<td>14</td>
<td>10.3</td>
</tr>
<tr>
<td>1–3</td>
<td>270</td>
<td>CMF</td>
<td>23</td>
<td>13</td>
<td>15+</td>
</tr>
<tr>
<td>4</td>
<td>794</td>
<td>Tamoxifen</td>
<td>31</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>448</td>
<td>Tamoxifen</td>
<td>46</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>183</td>
<td>CMF</td>
<td>20</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>112</td>
<td>CMF</td>
<td>51</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

*DBCG = Danish Breast Cancer Group; SECCSG = Southeast Cooperative Study Group; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; CA = cyclophosphamide, doxorubicin.
successfully managed with systemic therapy in whom sterilization of residual locoregional disease (foci for potential dissemination) could have the greatest impact. The 1997 results of the British Columbia trial demonstrated both statistically significant benefits in survival free of systemic disease and breast cancer-specific survival and borderline statistically significant benefit in overall survival following RT (12). With 2 years of additional follow-up, overall survival was statistically significantly improved following RT, with a greater relative reduction in mortality in the group with one to three positive lymph nodes versus the patients with four or more positive lymph nodes (38). In a combined analysis of DBCCG 82b and 82c in patients with at least eight lymph nodes examined, results also indicated that the greatest survival benefit occurred in patients with the least tumor burden. Survival was greatest following RT in women with smaller tumors and fewer positive lymph nodes compared with women with larger tumors and many involved lymph nodes (Overgaard M: personal communication).

The results of the Danish and Canadian trials would suggest that all lymph node-positive patients with operable breast cancer should receive RT to improve breast cancer-specific and overall survival. However, given the surgical limitations of these studies, particularly the Danish trials, caution should be used with generalizing these recommendations to U.S. practice. This is evident particularly in the group with one to three positive lymph nodes, in whom the risk of LRF was 30% in DBCCG 82b (14) compared with a 13% risk recently reported from the U.S. ECOG trials (19). Because of these concerns, a new intergroup trial, sponsored by the Southwest Oncology Group, has recently opened in this country, randomly assigning women with one to three positive axillary lymph nodes to RT or observation following mastectomy and adjuvant chemotherapy (Fig. 1). Patients must have a minimum of 10 lymph nodes dissected. The target accrual is 2500 women over a 5-year period, which is powered to detect a hazard ratio of 1.33, which corresponds to a 5.5% survival difference at 10 years. Primary endpoints will be both overall survival and disease-free survival, with a secondary endpoint of locoregional control.

TREATMENT GUIDELINES FOR OPTIMAL LOCOREGIONAL CONTROL

Results from adjuvant therapy trials that have studied the effect of systemic therapy on locoregional control have been contradictory. While some (39–41) have shown a reduction in the risk of LRF with chemotherapy and tamoxifen, others (42,43) have shown essentially no effect on local control. Perhaps the most comprehensive data can be obtained indirectly from the overview (16). In the published analysis of the proportional effect of RT on isolated local recurrence (16), RT produced essentially identical reductions in LRF in patients treated with and without chemotherapy and/or tamoxifen, suggesting that systemic therapies had very little effect on the proportional reduction of locoregional recurrence.

Locoregional patterns of failure without RT identify the chest wall as the most common site of failure. As shown in Table 2, over half of all LRF occur at the chest wall, with the mastectomy scar and the surrounding skin at greatest risk for recurrence (44). The second most common locoregional site following level I–II axillary dissection in most series is the supraclavicular and infrachlavicular region, with as many as 41% of all LRF occurring in this region (19,21,45,46).

U.S. surgical series of lymph node–positive patients (19,21) have shown the absolute risk of axillary failure to be 2%–4% at 10 years following level I–II axillary dissection. Therefore, full axillary RT is not generally recommended following an adequate dissection. The lower axillary bed, in the region of the tail of the breast, is included in the chest wall fields, and the supraclavicular field includes the apex of the axilla (the infrachlavicular region). The remaining portion of the previously dissected axilla would also be irradiated in a full axillary field, which could increase the risk of arm edema, as discussed below. For these reasons, routine full axillary irradiation is generally discouraged following adequate axillary surgery.

The question of whether to incorporate the internal mammary lymph nodes (IMNs) in the RT port has been, and continues to be, vigorously debated. Although previous surgical studies that included internal mammary lymph node dissection have demonstrated pathologic involvement in up to 37% of lymph node–positive breast cancers with inner or central primary tumors (47), clinical evidence of recurrence, as shown in Table 2, is low. Thus, treatment to the IMNs is difficult to justify on the basis of regional patterns of failure. It should be noted, however, that follow-up imaging studies of the IMNs to detect IMN recurrence are not done routinely; therefore, IMN failures may be substantially underreported.

Multiple randomized trials have been performed comparing prophylactic IMN irradiation or resection with observation; the largest of these trials are shown in Table 3. Although some trials have shown trends in favor of patients treated to the IMNs (2,4,48,49), no statistically significant benefit in disease-free or overall survival has been demonstrated to date, but follow-up has been limited in recent trials. Previous studies (18) have shown that 50% of parasternal recurrences occur 10 years or more following surgery, so long-term follow-up is needed to determine rates of IMN failure. Subset analyses (48,50) have suggested statistically significant survival benefits in lymph node–positive patients with medial/central primary tumors. These analyses, however, are subject to criticism of subgroup selection. Therefore, to study the value of internal mammary and medial supraclavicular (SCV) RT with contemporary RT techniques and systemic therapies, the European Organization for Research and Treatment of Cancer (EORTC) has sponsored a trial, randomly assigning women with positive axillary lymph nodes or negative lymph nodes with medial/central lesions to IMN and medial SCV RT or no RT to the IMN and SCV regions. The endpoints of the study are time to locoregional recurrence, distant metastases, and death. To detect a 5% difference in survival, a total of 3780 patients will be randomly
assigned to receive treatment. A second open trial sponsored by the National Cancer Institute of Canada is also studying the value of regional irradiation in patients treated with breast conservation. Patients must have either tumors with positive lymph nodes or high-risk lymph node-negative disease designated as T3 disease or T2 primary tumors with fewer than 10 lymph nodes removed and a primary lesion that is either ER negative or high grade or has evidence of lymphovascular invasion. The risk both of rib fracture and of brachial plexopathy is extremely low. Rib fractures occur in less than 3% of patients treated to the breast and chest wall, with a median time to fracture of approximately 12 months (51). In a series from the Joint Center for Radiation Therapy (JCRT), the incidence of rib fracture correlated with machine energy and breast dose, with statistically significantly more fractures occurring with 4-MV beams compared with 6- or 8-MV beams and with doses greater than 50 Gy (51). Chemotherapy increased the rate of rib fracture when the breast dose was less than 50 Gy. In all cases, fractures healed without intervention. Permanent brachial plexopathy from radiation to a supraclavicular and axillary apex field occurs in less than 1% of patients with doses less than or equal to 50 Gy in 2-Gy fractions. Factors shown to increase the incidence of plexopathy are the use of a supraclavicular field, an axillary dose greater than 50 Gy, the use of chemotherapy (51), and daily fractions in excess of 2 Gy (52).

In summary, on the basis of current evidence, locoregional failure patterns of breast cancer recurrence after mastectomy are treatment-related risk factors that affect the risk of arm edema (53–57). Researchers from the Royal Marsden Hospital, Sutton Surrey, UK, found that the risk of subjective lymphedema was 8% after axillary RT only, 9% after axillary sampling and axillary RT, 7% after axillary clearance only, and 38% after axillary clearance and RT (P<.001) (53). Larson et al. (56) also reported a 37% risk of arm edema following full dissection and axillary RT. In a complication analysis of the Danish postmastectomy trials, Hejris et al. (55) reported a statistically significant in-

### Table 2. Locoregional failure patterns of breast cancer recurrence after mastectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Chest wall (%)</th>
<th>Supraclavicular (%)</th>
<th>Axilla (%)</th>
<th>Internal mammary (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG (19)</td>
<td>420</td>
<td>244 (58)</td>
<td>158 (38)</td>
<td>82 (20)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Mallinckrodt Institute of Radiology (45)</td>
<td>224</td>
<td>156 (70)</td>
<td>54 (24)</td>
<td>28 (12)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>University of Pennsylvania (46)</td>
<td>128</td>
<td>106 (83)</td>
<td>28 (19)</td>
<td>14 (11.3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>The University of Texas M. D. Anderson Cancer Center (21)</td>
<td>124</td>
<td>122 (98)</td>
<td>51 (41)</td>
<td>21 (17)</td>
<td>—</td>
</tr>
<tr>
<td>Mt. Sinai Medical Center (84)</td>
<td>124</td>
<td>95 (77)</td>
<td>14 (11)</td>
<td>26 (21)</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>

*ECOG = Eastern Cooperative Oncology Group.

### Table 3. Results of randomized trials comparing internal mammary lymph node prophylaxis to observation

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>% disease-free survival</th>
<th>% overall survival</th>
<th>F/U, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romestaing et al. (85)</td>
<td>1281</td>
<td>83</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Morimoto et al. (86)</td>
<td>192</td>
<td>—</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Meier et al. (48)</td>
<td>112</td>
<td>—</td>
<td>—</td>
<td>74</td>
</tr>
<tr>
<td>Fisher et al. (B04) (2)</td>
<td>717</td>
<td>48</td>
<td>42</td>
<td>59</td>
</tr>
<tr>
<td>Host et al. (4)†</td>
<td></td>
<td>Central/medial tumors</td>
<td>86</td>
<td>60 (P = .03)</td>
</tr>
<tr>
<td>Oslo II, stage I</td>
<td>356</td>
<td>71</td>
<td>78</td>
<td>77</td>
</tr>
<tr>
<td>Oslo II, stage II</td>
<td>186</td>
<td>57</td>
<td>43 (P = .04)</td>
<td>58</td>
</tr>
<tr>
<td>Lacour et al. (49)</td>
<td>1453</td>
<td>56</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>Institut Gustav-Roussy (55)</td>
<td></td>
<td>N+ central/medial tumors</td>
<td>53</td>
<td>28 (P = .05)</td>
</tr>
<tr>
<td>Palmer and Ribeiro (87)</td>
<td></td>
<td>Lymph node negative</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>460</td>
<td>—</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

*Rx = radiotherapy or surgical prophylaxis; Obs = observation; F/U = follow-up.
†Values extrapolated from actuarial curves.

**POTENTIAL COMPLICATIONS OF TREATMENT**

Potential long-term complications following RT and chemotherapy after mastectomy include rib fracture, brachial plexopathy, arm edema, pneumonitis, cardiac effects, and second malignancies. Each will be discussed briefly.

In summary, on the basis of current evidence, locoregional radiation following mastectomy is recommended for patients at high risk of recurrence. Radiation should be delivered to the areas most at risk, including the chest wall, supraclavicular lymph nodes, and axillary apex when more than four axillary lymph nodes are involved. Full axillary RT is not routinely recommended to an adequately dissected axilla. Consensus has not been reached regarding treatment to the internal mammary region. This decision is left to the discretion of the treating radiation oncologist while trials designed to determine the value of treatment are in progress.
creases in the subjective assessment of lymphedema following full axillary RT and partial axillary dissection compared with surgical controls. In radiation series where regional treatment has been restricted to a supraclavicular and axillary apex field following a level I–II axillary dissection, rates of edema have been low (58). Pierce et al. (58) from the University of Michigan, Ann Arbor, reported a 3% rate of arm edema after limited supraclavicular and infraclavicular RT. Therefore, full axillary RT should be discouraged following complete level I–III axillary dissection. Limitation of axillary RT to the apex of the axilla following level I–II dissection appears to minimally increase the risk of edema beyond that observed following surgery only.

The overall risk of pneumonitis is approximately 5% and is generally transient (59). The risk increases, however, with increasing lung volume in the tangent fields and with treatment to the supraclavicular, axillary apex, and internal mammary regions (59,60). The risk also appears to increase with the use of concurrent chemotherapy. Lingos et al. (59) found the risk of pneumonitis to be 1.3% for patients who were treated to an SCV field and who received sequential chemotherapy versus 9% for those receiving concurrent chemotherapy (P = .002). Therefore, although the overall risk of pneumonitis is low, the increase observed with concurrent chemotherapy and RT should be considered when contemplating sequencing strategies of locoregional and systemic therapies.

Potential radiation-induced second malignancies after locoregional RT include the development of in-field sarcomas, lung cancer, leukemia, and contralateral breast cancers, all of which are rare. The risk of developing a sarcoma in the RT field has been estimated by Kurtz et al. (61) from the Marseilles Cancer Institute, France, to be nine cases per 100,000 patient-years. Ten-, 20-, and 30-year actuarial estimates reported by Taghian et al. (62) from the Institut Gustav-Roussy, Villejuif, France, were 0.2%, 0.43%, and 0.78%, respectively.

Modest increases in the absolute rate of lung cancers have been observed following RT (63). Neugut et al. (64) found a relative risk (RR) of 2.0 among patients treated with RT who survived 10 or more years from diagnosis. A case–control study using Connecticut Tumor Registry data demonstrated a statistically nonsignificant increase in lung cancer cases in nonsmokers who received RT and a statistically significant increase among treated smokers (63,64). A study by Inskip et al. (65) found an RR of 2.8 of lung cancer among patients who received RT for breast cancer at least 10 years earlier. In absolute terms, nine cases of radiation-induced lung cancer would be expected in 10,000 women surviving at least 10 years. Therefore, the absolute number of women potentially affected with radiation-induced lung cancer is very low. However, smoking cessation interventions, which could further reduce this incidence, should be encouraged strongly.

The association of RT with the risk of acute nonlymphocytic leukemias (ANLL) appears to be related to both volume of bone marrow in the irradiated field and dose delivered (66). In a review by Shapiro and Recht (66), the RR of ANLL appeared to be 0.86–3.7 after RT, compared with an RR of 1.3–11.5 after chemotherapy. A higher RR was demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 and B-06 trials, with a 10-fold RR following RT (and a 24-fold RR following chemotherapy) (67). This represented, however, only four cases, compared with the expected incidence of 0.39. Therefore, collectively, the absolute risk of ANLL associated with RT is very low, especially with limited bone marrow in the radiation port.

Limited data suggest a slight excess of contralateral breast cancers following RT above the expected 0.3%–1.0% annual risk (68,69). Age at time of exposure appears to be a risk factor in some series, with younger women at higher risk for a contralateral breast cancer. In the study by Boice et al. (70), the RR of contralateral breast cancer was 1.59 in women less than 45 years of age at treatment, whereas women 45 years old and older showed no effect (RR = 1.01). Although the risk of radiation-associated contralateral breast cancers is extremely low, measures to reduce scatter to the opposite breast, such as omission of a medial wedge from tangent fields (71), should be used to reduce contralateral breast dose.

The most recent update of the meta-analysis of RT trials (16) demonstrated a highly statistically significant benefit in breast cancer-specific survival following RT that was largely offset by an increase in vascular deaths. Although the cardiac component of the vascular deaths could not be specifically defined, almost certainly a large percentage of these vascular deaths were cardiac in origin. Previous reports (72–74) have described the excessive total doses and dose/fractions delivered to large volumes of the heart in the earlier trials, which dominate the results of the overview. When Rutqvist et al. (75) reanalyzed the doses received in the Stockholm trial according to the estimated doses to the myocardium, patients who received the highest doses had a statistically significantly increased rate of death caused by ischemic heart disease when compared with surgical control subjects (76). More recent studies (77,78) examining the risk of cardiac events using modern radiation techniques have not found differences by latency; however, increased follow-up is needed because of the latency of radiation-induced cardiac disease. Højris et al. (79) analyzed the cardiac events in patients randomly assigned in Danish trials 82b and 82c and reported a relative hazard of morbidity from ischemic heart disease of 0.86 for the RT versus no RT patients and a hazard for death from ischemia of 0.84 after 12 years. Therefore, it appears that careful treatment planning and use of low-energy electrons to treat the chest wall and internal mammary lymph nodes have resulted in no increase in cardiac toxicity in the Danish studies at 12 years. Further follow-up will be needed to verify continued constant hazard rates with time.

Despite improvements in RT planning techniques, the potential for additive cardiac toxic effects of RT and systemic therapies mandates careful radiation treatment planning. A study reported by Shapiro et al. (80) demonstrated the potential for cardiac toxicity with high-dose doxorubicin and cardiac irradiation, with an eight- to 10-fold risk of cardiac toxicity at a dose of 450 mg/m² of doxorubicin and RT compared with a negligible risk at a dose of 225 mg/m². With the known cardiac effects of doxorubicin and trastuzumab (currently in trials for adjuvant use) and the radiosensitizing effects of paclitaxel (81–83), RT planning using computed tomography-based systems should be used to minimize cardiac exposure. Funding for continued advances in RT treatment planning should be supported to maximize survival gains.

**SUMMARY**

Randomized trials have demonstrated that locoregional radiation following mastectomy in patients treated with systemic therapy reduces locoregional recurrence and increases survival.
The majority of patients in these trials were at high risk for LRF. On the basis of the results of these studies, locoregional radiation is recommended to these patients following systemic therapy. The role of locoregional radiotherapy following mastectomy in patients with one to three axillary lymph nodes is currently undefined and is being evaluated in an ongoing randomized trial. Modern techniques should be used to avoid excessive radiation to the heart, lungs, and other normal tissues. Locoregional radiotherapy should be directed to the chest wall, supraclavicular lymph nodes, and axillary apex. The role of IMN irradiation is unclear. Trials are now in progress to evaluate the potential benefit of IMN treatment.

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