Defining the Role of Post-Mastectomy Radiotherapy: The New Evidence

Review Article [1] | July 01, 1996
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In an early meta-analysis of the post-mastectomy radiotherapy trials, the use of obsolete radiotherapy techniques resulted in increased cardiac mortality. With maturation of these data and inclusion of more recent

Introduction

The current role of post-mastectomy radiotherapy as an adjuvant treatment in stage II breast cancer has been challenged. Although adjuvant radiation was once an established therapy in the management of breast cancer, the routine use of systemic therapy in patients at significant risk for distant (and local) dissemination has caused some to question the need for locoregional radiotherapy. Several issues must be considered when weighing the relative merits of adjuvant locoregional radiotherapy:

- Can systemic therapy improve locoregional control comparable to that achieved with radiotherapy, such that the addition of post-mastectomy radiotherapy offers no further benefit?
- Are there subgroups of women at high risk for locoregional failure who would particularly benefit from the use of post-mastectomy radiotherapy?
- If post-mastectomy radiotherapy improves locoregional control in the presence of chemotherapy, could this have an impact on overall survival?

To begin to understand the importance of post-mastectomy radiotherapy in the current management of breast cancer, it is necessary to first look at the role this modality has played prior to the use of systemic treatment. Also, when formulating current recommendations for the use of post-mastectomy radiotherapy, it is important to extrapolate the lessons learned from the early trials.

Failure Patterns Following Mastectomy Alone

Analyses of locoregional failure have shown the chest wall to be the most common site of failure [1-3]. Halverson et al reported the chest wall to be the site of isolated locoregional recurrence in 60% of patients with a locoregional failure, with an additional 10% of patients having the chest wall as a component of failure, so that the chest wall was involved in 70% of the locoregional failures [1]. The mastectomy scar is at greatest risk for recurrence [4]. Donegan et al reported the scar or grafted area to be the most frequent site of chest wall involvement, accounting for 42% of such recurrences [4]. In most series, the supraclavicular/infraclavicular nodes are the second most common site of locoregional failure, with involvement as a single site in 10% to 20% patients. Clinical recurrences occur less frequently in the internal mammary nodes or in the axilla. From 5% to 10% of patients present with an isolated failure at each site in an adequately dissected axilla [5].

Predictors of Locoregional Failure Following Mastectomy Alone

Additional analyses have identified various factors that are predictive of increased locoregional failure.

Positive Axillary Nodes--The finding of positive axillary nodes has been shown consistently to be the major predictor of chest wall failure [4,6,7]. Haagensen reported in one of the earliest series, factors that predicted a local recurrence following mastectomy [6]. Of 935 patients with either stage
I or II disease treated with radical mastectomy and followed for at least 10 years, axillary node involvement was closely related to the risk of chest wall recurrence, with recurrence rates up to 42% in patients with four or more nodes positive. Donegan et al performed a similar analysis of locally recurrent breast cancer following radical mastectomy [4]. Among the 704 women studied, only 6.5% of patients with histologically uninvolved axillary nodes had a local recurrence at 5 years, as compared with 26% of women with pathologically involved nodes. The percentage of local recurrence was directly correlated with the absolute number of positive nodes: Involvement of 1 to 3 nodes was associated with a 10% to 15% recurrence rate at 5 years; this rate increased to 25% to 38% with 4 to 7 positive nodes and to 43% or higher with 8 or more positive nodes.

In a trial from Stockholm, in which women were randomized to post-mastectomy radiotherapy, histologic lymph node status was an independent predictor of local recurrence. The relative risk for local failure was three times greater among women with positive nodes than among those with negative nodes [7]. Other factors have also been associated with increased locoregional failure following mastectomy in the absence of systemic therapy. The size of the primary lesion has been correlated with local recurrence in some series [4,8-10]. Donegan and colleagues found a direct association between tumor diameter and local recurrence, with 0% of patients with tumors less than 1.0 cm having a local failure, increasing to 16% for tumors 3.0 to 3.9 cm, 27% for lesions 5.0 to 5.9 cm, and greater than 30% for tumors exceeding 6.0 cm [4]. This study did not correct for the presence of positive axillary nodes, however, in determining this association.

In series reported by Rosenman et al [8] and Valagussa et al [9], tumor size was strongly correlated with locoregional recurrence in node-positive patients. Pathologic factors found in the Cancer Research Campaign Trial to independently predict for increased locoregional recurrence included the size of the primary lesion [10]. Distance of the tumor to the pectoralis fascia may also affect local failure. In one series examining local recurrence as a function of the distance to the deep resection margin, seven of eight patients with local recurrence had a margin of 0.5 cm or less [11]. Other factors that may also have an impact on chest wall recurrence include lymphatic invasion and tumor grade [10,12].

**Importance of Locoregional Control**

Quality of life can be severely compromised by a locoregional failure following mastectomy. Subsequent rates of locoregional control with radiotherapy following a recurrence have been disappointing. Reported control rates have ranged between 25% and 76%, depending on tumor bulk and resectability, with an average control rate of 50% [1-3,5]. Thus, even with optimal radiotherapy, 50% of patients experiencing a locoregional failure will die with uncontrolled locoregional disease. This argues strongly in favor of the delivery of prophylactic radiotherapy following mastectomy for maximal local control. In recent series in which radiotherapy has been delivered to high-risk patients in conjunction with chemotherapy, isolated locoregional recurrences have been reduced to 5% to 10% [13].

It has also been suggested that increased locoregional control influences survival. In every surgical series of stage I or II breast cancer to date, locoregional therapy as sole therapy has been curative in a majority of node-negative patients and a minority of node-positive women [4,6,9]. Therefore, a finite percentage of early-stage breast cancers are confined locoregionally and are cured by definitive locoregional treatment. Conversely, a minority of node-negative women and a majority of node-positive women whose disease is locally controlled develop sites of distant dissemination. Sequential National Surgical Adjuvant Breast Project (NSABP) studies comparing locoregional therapies have shown little correlation between local control and overall survival [14,15]. Based on these results, Fisher et al hypothesized that breast cancer is a systemic disease at presentation, and that local control has little to no impact on survival. An alternative hypothesis proposed by Hellman suggests that breast cancer is a heterogeneous disease in which subsets of women present with systemic disease, whereas others have disease restricted to locoregional sites at diagnosis [16]. In the latter group, locoregional control would surely influence outcome. Therefore, for reasons including both quality of life and, potentially, overall survival, the maintenance of locoregional control is an important goal.

**Randomized Trials of Mastectomy With or Without Radiotherapy**
Multiple randomized trials have compared local control and overall survival in women treated with radical mastectomy, modified radical mastectomy, or total mastectomy followed by either post-mastectomy radiotherapy or observation [10,14,17-23]. As shown in Table 1, these trials extend over a wide range of time, with the majority conducted 20 to 30 years ago. Therefore, it is not surprising that the techniques and equipment used to administer radiotherapy in these trials are not comparable to those employed today. Many of the earlier trials used orthovoltage machines with energies inadequate to treat the entire depth of the target tissues at risk. Some trials were designed to treat only the regional lymph nodes and excluded the chest wall from the treatment volume. As discussed above, the chest wall is the major site of locoregional failure; therefore omission of the chest wall from the treatment field would be expected to result in increased locoregional recurrence. Other criticisms of these trials include the use of inadequate total doses and large daily fraction sizes, and inappropriate patient selection. As demonstrated in Table 1, the total doses delivered often were below the dose adequate to control microscopic disease, ie, 45 to 50 Gy [24]. Fractionation schemes commonly involved daily doses in excess of 2 Gy, which could increase chronic morbidity, most notably, to the heart and lung. These trials typically included patients at low risk for locoregional recurrence, which would have reduced their statistical power to demonstrate an advantage for post-mastectomy radiotherapy. Also, in many of the total mastectomy trials, patients underwent only axillary node sampling, which could have underestimated pathologic nodal involvement.

Early Analyses of Trial Results—Despite these limitations in the design and execution of the post-mastectomy trials, every trial evaluating locoregional control still demonstrated a benefit from the addition of radiotherapy; the magnitude of this benefit ranged from 8% to 20%, depending on the length of follow-up. In early analyses of the results, however, the favorable effect of radiotherapy on locoregional control did not translate into a significant overall survival advantage. In fact, a meta-analysis of 10-year survivors from eight post-mastectomy radiotherapy trials begun prior to 1975 demonstrated a decreased survival among women who received adjuvant radiotherapy, compared to controls [25]. A subsequent report presented cause-specific mortality data for all patients who died more than 10 years after entry into the trials and provided updated follow-up on all women entered into these studies [26]. Only cardiac-related causes of death were increased among patients who received radiotherapy. The increase in cardiac deaths was attributed to radiotherapeutic techniques no longer in use. The update demonstrated that this negative effect on overall survival was almost balanced, however, by a reduction in breast cancer deaths among irradiated patients entered into the more recent trials. Specifically, women who received radiotherapy in the Stockholm, Manchester Regional, Cancer Research Campaign, and NSABP trials had a survival benefit relative to controls [10,14,20,21]. The updated analysis supported a causal relationship between maximal local control achieved with adjuvant radiotherapy and improved cancer-specific survival [26].

Early Breast Cancer Trialists' Overview—The Early Breast Cancer Trialists' Collaborative Group recently published an overview of the effects of radiotherapy and surgery in early-stage breast cancer [27]. Included in this analysis were results of 35 trials randomizing a total of 17,273 women to either radiotherapy plus surgery or surgery alone. As expected, radiotherapy produced a highly significant reduction in the rate of isolated local recurrences. In the 32 trials that reported site of recurrence, 6.7% of women receiving radiotherapy developed an isolated local failure, as compared with 19.6% of patients in the surgery-only groups (odds ratio, .33). Information was available from 28 trials on causes of death. Among the women assigned to receive radiotherapy, 34.1% died of breast cancer, as opposed to 36.9% of controls; this yielded an odds ratio of .94 in favor of radiotherapy (P = .03). Although overall mortality was 40.3% with radiotherapy vs 41.4% without it, this difference did not achieve statistical significance due to non-breast cancer deaths. However, the reduction in breast cancer-related deaths among women treated with radiotherapy was, again, suggestive of improved breast cancer-specific survival due to maximal local control.

Improved Survival vs Cardiac Mortality: The Stockholm Study—The competing issues of improved survival secondary to radiotherapy and the potential for cardiac mortality associated with radiotherapeutic technique are perhaps best contrasted in the Stockholm study [20]. In this study, premenopausal and postmenopausal women either received preoperative radiotherapy or postoperative radiotherapy or were observed following modified radical mastectomy. For the earlier patients enrolled in the study who received radiotherapy, the chest wall was treated with electrons, and the breast and regional nodes, including bilateral internal mammary nodes, were treated with cobalt-60 therapy. In the latter half of the study, the contralateral internal mammary nodes were
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omitted from the radiotherapy field. As shown in Table 1, with a mean follow-up of 16 years, the rate of locoregional recurrence as a first failure was only 4% in both the preoperative and postoperative arms, as compared with 20% among the controls (P less than .001). The reduction in locoregional recurrences was observed in both node-negative and node-positive women. The risk of distant failure was decreased in both the preoperative and postoperative radiotherapy groups, with a significant benefit in relapse-free survival following radiotherapy. This reduction in distant metastases and subsequent reduction in breast cancer deaths was restricted to the node-positive group. Among patients treated with cobalt-60 to left-sided lesions and regional nodes, a significant increase in ischemic heart disease was seen compared to surgical controls. No such increase was seen among patients who underwent cobalt-60 therapy of right-sided cancers or those with left-sided cancers treated with electrons. Therefore, omission of the heart from the radiation beam, in addition to delivery of a therapeutic radiation dose, resulted in improved survival secondary to post-mastectomy radiotherapy.

Reanalysis of the Stockholm Data—Arriagada et al recently reanalyzed the Stockholm data to determine the effect of local recurrence on distant dissemination [7]. The authors used a competing risk model to estimate the occurrence of all events leading to an overall event rate. This approach took into account all possible occurrences, including local failure, distant failure, new primary malignancies, contralateral breast cancers, and intercurrent deaths, such that an event-free survival could be calculated. Using 15-year cumulative incidence rates for all patients in the study, the authors showed a fivefold decrease in the risk of local recurrence with radiotherapy (P less than 10-4). In the analysis of total events, radiotherapy also significantly reduced the rate of distant metastases (P = .04). An analysis of patients with pathologically negative nodes indicated that radiotherapy reduced local failure 10-fold compared to unirradiated controls but had no effect on the rate of distant recurrence. This contrasted with the results in node-positive patients, in whom radiotherapy produced a significant decrease not only in local recurrence but also in distant failure. In a Cox regression analysis of factors predictive of distant dissemination, both tumor size and histologic node size were predictive of distant metastases, with relative risks of 1.35 and 2.83, respectively. A local recurrence was highly predictive of distant recurrence, with a relative risk of 6.0. This analysis suggested that the decrease in distant metastases was related to the prevention of local recurrence. This finding, in addition to the results of the Cox analysis in node-positive women, suggested that post-mastectomy radiotherapy in patients with positive nodes may decrease the rate of distant metastases by preventing local recurrences and avoiding secondary dissemination. Thus, this analysis further supports the contribution of locoregional control to improved survival.

Locoregional Failure After Mastectomy and Adjuvant Systemic Therapy

Since systemic therapy has been shown to improve disease-free and overall survival in women with stage II disease, the question has been raised as to whether systemic therapy can prevent locoregional recurrence following mastectomy. Chemotherapy—Examination of the results of trials in which women have been randomized to receive chemotherapy following mastectomy demonstrates a wide variation in loco-regional recurrence rates. For example, in an update of the Guy's/Manchester trial of adjuvant cyclophosphamide, methotrexate, and fluorouracil (CMF) in node-positive breast cancer, premenopausal patients who received CMF had a significant improvement in locoregional control, with a 5-year actuarial locoregional recurrence rate of 18%, as compared with a 44% rate in control patients [28]. Postmenopausal patients who received CMF did not benefit with respect to locoregional control compared to controls. The 10-year results of the NSABP B05 trial, in which women with positive axillary nodes were randomized to receive melphalan ([l-phenylalanine mustard [Alkeran]]) also demonstrated a locoregional benefit for those receiving melphalan. Locoregional recurrence was the initial site of failure in 24% of patients receiving placebo vs 14% of those who received melphalan [29]. A trial conducted by the West Midlands Oncology Association in which patients with positive axillary nodes were randomized to receive Adriamycin, vincristine, cyclophosphamide, methotrexate, and fluorouracil (AVCMF) demonstrated a modest benefit in locoregional control with adjuvant chemotherapy; 34% of patients treated with AVCMF experienced a locoregional failure as a first failure, as opposed to 40% of controls [30].
In a 20-year update of the Milan trial, which randomized node-positive women to CMF, minimal benefit was shown for women receiving adjuvant chemotherapy. The first failure occurred locoregionally in 13% of women treated with CMF vs 15% in the control group [31]. Thus, while some trials have shown some improvement in locoregional control with adjuvant chemotherapy, others have not reproduced these findings. Nonetheless, even those trials that have shown a reduction in locoregional failure have still generally demonstrated increased rates of locoregional recurrence.

Dose intensity does not appear to further reduce locoregional failure [32,33]. Among patients entered into the Cancer and Leukemia Group trial 8782 who underwent bone marrow transplantation, three (33%) of the nine patients who did not receive radiotherapy developed a chest wall recurrence. This compared with 1 failure (3%) in 34 women who received the prescribed course of radiotherapy (P = .02).

**Tamoxifen (Nolvadex)** may also reduce the risk of locoregional failure following mastectomy relative to controls. In Trial III of the International (Ludwig) Breast Cancer Study Group, node-positive post-menopausal women were randomized to receive either endocrine therapy with tamoxifen and continuous low-dose prednisone (P + T) for 12 months, chemoendocrine therapy with cyclophosphamide, methotrexate, fluorouracil, prednisone, and tamoxifen (CMFP + T) for 12 cycles, or observation [34]. With a median follow-up of 13 years, 34% of women in the observation group have experienced a locoregional recurrence as a first failure, as compared with 21% in the endocrine group, and 14% in the chemoendocrine group.

In a Swedish study of postmenopausal women with either positive axillary nodes or primary tumors greater than 3 cm, patients were randomized to postoperative radiotherapy (RT); RT plus 2 years of tamoxifen (RT + T); adjuvant chemotherapy consisting of either 12 cycles of CMF or Leukeran, methotrexate, and fluorouracil (LMF); or CMF/LMF and tamoxifen (CMF/LMF + T) [35]. Locoregional failure was reported by total incidence of events rather than first failure. With a mean follow-up of 6.5 years, the locoregional failure rate was 32% for CMF/LMF, 20% for CMF/LMF + T, 13% for RT, and 12% for RT + T. Radiotherapy significantly reduced the rate of locoregional failure compared to chemotherapy, and the addition of tamoxifen reduced the number of failures compared to chemotherapy alone. Tamoxifen did not appear to impact further on locoregional failure among women receiving radiotherapy.

**Predictors of Locoregional Failure After Mastectomy and Adjuvant Chemotherapy**

Analyses have examined the factors predictive of locoregional failure following chemotherapy. Stefanik et al retrospectively reviewed the outcome of 117 women who received CMF following either radical or modified radical mastectomy [36]. The 5-year actuarial locoregional failure rate was 19%, with a 9% risk of locoregional failure with one to three positive nodes vs 36% locoregional failure with four or more positive nodes (P less than .01). The risk of local failure also correlated with the size of the primary; actuarial local failure rates were 15%, 25%, and 27% for T1, T2, and T3 tumors, respectively.

A review of 627 women entered into Eastern Cooperative Oncology Group adjuvant chemotherapy trials of methotrexate-containing regimens found that 11% of patients had an isolated locoregional failure within the first 3 years, which represented 31% of the failures [37]. Patients with four to seven positive nodes or tumor size equal to or more than 5 cm had a chance of developing an isolated locoregional recurrence that was almost equal to the risk of distant metastasis. Pisansky et al studied the patterns of failure in 564 patients with axillary node-positive breast cancer who received cyclophosphamide, fluorouracil, and prednisone with or without tamoxifen following mastectomy [38]. The 8-year cumulative incidence of initial locoregional relapse was 20%. In a multivariate analysis, pathologic tumor stage (T3a), number of involved axillary nodes, and estrogen-receptor content were independent predictors of isolated locoregional failure. Sykes et al analyzed locoregional outcome following adjuvant doxorubicin and cyclophosphamide in patients with stage II or III breast cancer [39]. With a median follow-up of 60 months, the overall rate of isolated locoregional failure was 15%. A multivariate analysis demonstrated that increasing stage was a predictor of locoregional failure.

**Summary**--All these data indicate that the risk factors for locoregional recurrence following mastectomy and adjuvant chemotherapy appear to be similar to the predictors of failure in the absence of chemotherapy. Patients with positive axillary nodes and T3 tumors remain at risk for locoregional failure despite the use of adjuvant chemoendocrine or endocrine therapy. We therefore...
recommend that patients with T3 tumors, four or more positive axillary nodes, and positive surgical margins undergo post-mastectomy radiotherapy. As more information becomes available on the patterns of failure in patients with one to three positive nodes, the role of post-mastectomy radiotherapy in this group of women may need to be reassessed.

Randomized Trials of Mastectomy and Adjuvant Chemotherapy With or Without Radiotherapy

Numerous randomized trials have compared radiotherapy to observation following mastectomy and adjuvant systemic therapy [40-48]. These trials are summarized in Table 2. In each trial, the addition of radiotherapy reduced the rate of locoregional failure relative to controls. However, the majority of studies have shown no improvement in overall survival. Many of these trials included small numbers of women and had limited follow-up, which significantly reduced their statistical power. This discussion will focus on the three studies that either enrolled the greatest number of patients or have a minimum of 9 years’ median follow-up.

**Southeastern Cancer Study Group Trial**—The Southeastern Cancer Study Group randomized women with four or more positive axillary nodes to receive 12 cycles of CMF, 6 cycles of CMF, or 50 Gy of radiation to the chest wall and regional nodes followed by 6 cycles of CMF [45]. This trial was part of a larger investigation that also randomized patients with one to three positive axillary nodes to 6 vs 12 cycles of CMF without the option of radiotherapy. For patients with four or more positive nodes who were randomized to receive radiotherapy, treatment was delivered to the chest wall, axilla, internal mammary nodes, and supraclavicular fossa.

With a median follow-up of 10 years, there was a trend toward improved disease-free survival among women receiving six cycles of CMF with radiotherapy compared to those receiving six cycles of CMF alone. Relapses occurred in 75/122 (61%) of patients treated with six cycles of CMF only vs 57/117 (49%) of those also given radiotherapy (P = .07 [log rank comparison]). Survival did not differ significantly between the two treatment arms, but actuarial analyses suggested a trend in favor of radiotherapy.

**British Columbia Trial**—A randomized trial from British Columbia also compared the outcome of 318 women who received six cycles of CMF alone or together with locoregional radiotherapy [47]. Patients participating in this trial were premenopausal with either clinical stage I or II disease who had pathologically positive axillary nodes at the time of surgery. Those randomized to radiotherapy received comprehensive therapy to the chest wall and regional nodes after the fourth cycle of chemotherapy. Despite the small number of patients, which limited statistical power, a 12-year analysis demonstrated a significant improvement in disease-free survival for those randomized to the radiotherapy arm, with a 12-year disease-free survival of 57% following CMF and radiotherapy vs 63% following CMF only (P = .02). The corresponding survival rates were 57% for CMF and 60% for CMF plus radiotherapy (P = .09).

**Danish Trial**—The largest trial studying the benefit of post-mastectomy radiotherapy among women receiving adjuvant chemotherapy was conducted in Denmark [48,49]. Between 1982 and 1989, the Danish Breast Cancer Cooperative Group enrolled 1,708 premenopausal women into a trial randomizing patients to CMF with or without radiotherapy. Patients randomized to CMF alone received nine cycles, whereas those receiving combined-modality therapy received eight cycles of CMF, with the radiotherapy delivered sequentially after the first cycle of CMF. The majority of the patients in this study had positive axillary nodes and T1 or T2 lesions, although patients with node-negative tumors and T3 or T4 lesions were also included. Radiotherapy consisted of approximately 48 to 50 Gy to the chest wall, axilla, supraclavicular fossa, and internal mammary region. Design of the radiotherapy fields was based on CT planning to optimize beam arrangements. With a median follow-up of 9 years, the addition of radiotherapy significantly improved locoregional control, disease-free survival, and overall survival: The 9-year local failure rates with and without radiotherapy were 13% vs 40% (P less than .01), respectively; disease-free survival rates for the two treatment arms were 50% and 35%, respectively (P less than .01); and crude survival rates were 56% and 50%, respectively (P less than .01). Therefore, radiotherapy improved the absolute survival rate in node-negative premenopausal women already receiving adjuvant chemotherapy by 6%.

**Tamoxifen With and Without Radiation**—The Danish Breast Cancer Cooperative Group also conducted a randomized trial of tamoxifen with and without radiotherapy in high-risk postmenopausal women [48,49]. A total of 1,375 postmenopausal women less than 70 years of age received 30 mg/d of tamoxifen followed by comprehensive locoregional radiotherapy or observation. With 9-year median follow-up, there was a significant benefit in locoregional control and disease-free
survival with the combined endocrine and locoregional therapy. The rate of local failure with tamoxifen alone was 45%, as compared with 12% with the addition of radiotherapy (P less than .01), and disease-free survival was 31% with tamoxifen alone and 38% with combined-modality therapy (P less than .01). Although there was a trend toward improved survival with radiotherapy, the results were not statistically significant; crude survival rates were 45% and 50% with and without radiotherapy, respectively.

**Summary**--Thus, while all of the post-mastectomy radiotherapy trials show a benefit on locoregional control with the addition of radiotherapy to either chemotherapy or tamoxifen, the larger trials also show an improvement in disease-free survival and overall survival. This suggests that systemic therapy and radiotherapy individually provide benefit and that the combination of the two modalities maximizes the potential for improved disease-free and overall survival.

**Sequencing of Therapy**

The appropriate sequencing of post-mastectomy radiotherapy and chemotherapy is not well defined. Variations in delivery of treatment have included sequential therapy, concurrent treatment, and a "sandwich" approach, in which radiotherapy is delivered between successive cycles of adjuvant chemotherapy. Although the most common means of sequencing therapy in everyday practice has been to deliver radiotherapy following completion of chemotherapy, patients entered into the various randomized trials listed in Table 2 have received therapy using each of the possible treatment sequences. Despite this variation, the addition of radiotherapy has significantly improved locoregional control.

The two trials that have shown a significant benefit in either disease-free or overall survival, ie, the Danish Breast Cancer Cooperative Group trial [48,49] and the British Columbia trial [47], administered radiotherapy between chemotherapy cycles such that radiotherapy was delivered within 6 months of surgery. Since these trials were not designed to address the question of sequencing of therapy, no definitive conclusions regarding integration of therapy can be reached. The only randomized trial that directly addresses the question of integration of radiotherapy and chemotherapy has been reported in abstract form only [50]. In this trial from Spain, 248 node-positive women were randomized to receive either six cycles of CMF followed by post-mastectomy radiotherapy, radiotherapy first followed by CMF, or radiotherapy sandwiched between three cycles of CMF (ie, three cycles of CMF followed by radiotherapy followed by three cycles of CMF). Both local control and disease-free survival were significantly improved at 10 years among patients treated with the sandwich approach. Specifically, local control rates were 95% in the sandwich group vs 90% in the delayed chemotherapy group and 82% in the delayed radioactivity group (P = .02), and disease-free survival rates were 57%, 41%, and 46%, respectively (P = .05). Although these results support the value of delivering radiotherapy prior to completion of six cycles of chemotherapy, it is premature to conclude a definite advantage using this approach from one report alone. Additional studies are needed that specifically address the question of sequencing of therapy in the post-mastectomy setting.

**Radiotherapeutic Techniques**

As discussed above, in the early post-mastectomy radiotherapy trials, older techniques of radiotherapy delivery and altered fractionation schemes resulted in severe chronic morbidity, most notably, cardiac toxicity. In the recent update of the meta-analysis of post-mastectomy trials, which provided cause-specific mortality, standardized mortality ratios demonstrated that patients who receive post-mastectomy radiotherapy have a significant increase in cardiac mortality that exceeds 1.5 times the risk of controls [26]. Despite this increase, survival was improved in the more recent trials due to the reduction in breast cancer deaths. Therefore, reduction of radiotherapy-associated toxicity would result in a further increase in overall survival.

Current radiotherapy techniques differ significantly from those used in the early trials. In general, both the volume of heart irradiated and the dose delivered to the heart are significantly less than in the trials reviewed in the meta-analysis. The major variable determining the amount of heart and lung that will be included in the treatment field is the decision to treat the internal mammary nodes. The factors involved in deciding whether to irradiate the internal mammary nodes have been discussed elsewhere [51]. As shown in Figure 1, the proximity of the internal mammary region to the heart adds a level of complexity to the treatment planning process; the primary challenge is how to deliver a full dose to the internal mammary nodes while minimizing exposure to the heart. Computed tomographic studies in patients in whom the internal mammary nodes were not
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intentionally treated have demonstrated that on average, 0% of the heart is in the radiation field for a right-sided cancer vs approximately 12% for a left-sided lesion [52]. Outcome studies in which the internal mammary nodes were excluded from the radiation field have not shown an increase in cardiac morbidity compared to outcomes in women who did not receive radiotherapy [15,53,54]. For patients in whom the internal mammary nodes were intentionally treated, the percentage of heart included in the treatment field varies depending on the field arrangement. A detailed discussion of various techniques to be considered when incorporating the internal mammary nodes into the treatment field is presented elsewhere [51]. Three basic techniques are compared here for the purposes of discussion.

**Techniques for Including Internal Mammary Nodes**—In Figure 2, the internal mammary nodes are treated in concert with the chest wall in "deep" tangential photon fields. This approach provides uniform coverage of both regions and ease of technical set-up. However, the obvious disadvantage of this technique is incorporation of increased cardiac (for a left-sided lesion) and lung volume into the high-dose region, as well as inclusion of the medial aspect of the contralateral intact breast in the radiotherapy field.

Figures 3 and 4 show alternative plans for treatment of the same desired target volumes. In Figure 3, a combination of photons and electrons is used to treat the chest wall and internal mammary nodes. The chest wall is encompassed largely within the tangential fields, while the remaining medial chest wall and internal mammary nodes are treated by an electron field. Since electron radiotherapy delivers the dose only to a specified depth and then decreases rapidly to negligible levels, cardiac volume in the full-dose region is minimal. Figure 4 demonstrates the use of electron beams to encompass the entire target volume, which, depending on patient anatomy, could reduce the volume of both lung and heart in the high-dose region.

Although the treatment plans shown in Figures 3 and 4 deliver minimal dose to the heart and lung, they are less favorable dosimetrically than the deep tangents shown in Figure 2 due to inhomogeneity at the junction of the fields at surface and at depth. Far more sophisticated techniques are available that attempt to even out the areas of dose inhomogeneity while minimizing dose to critical structures. These include conformal moving-beam electron therapy (electron arc radiotherapy) and three-dimensional treatment planning techniques. Suffice it to say that no one plan is optimal for every patient. Treatment planning must be individualized on a case-by-case basis with the aid of CT-based planning systems such that beam arrangements can be optimized with respect to the target volumes and patient anatomy. In this way, maximal dose homogeneity can be delivered to the appropriate structures while minimizing radiation exposure to pulmonary and cardiac tissue. This is especially critical, as many women are receiving potentially cardiotoxic doxorubicin-based chemotherapy regimens that could further compromise cardiac reserve.

**Future Research**

Clearly, a great deal of controversy still surrounds the use of post-mastectomy chest wall irradiation. Proponents of post-mastectomy radiotherapy point to a lowering of chest wall failure rates, improvements in disease-free survival, reductions in the distant metastasis rate and the number of deaths from breast cancer, and the overall survival advantage demonstrated in the recent Danish study [48,49]. Detractors point to a failure to show a consistent survival advantage attributable to chest wall irradiation even in a large meta-analysis [27]. They also note that the "Halstedian" concept, which holds that variations in local therapy would have a measurable impact on overall outcome, has been discarded. However, it may be true that local therapy influences survival in some patients. Thus, the Halstedian and alternative hypotheses to explain breast cancer spread may not be an either/or proposition; rather, a combination of these mechanisms may be responsible for the spread of this cancer [16,55]. Certainly, there may be a group of patients who have been rendered free of systemic disease by adjuvant chemotherapy only to have minimal locoregional disease still present. Such is the case in the setting of high-dose chemotherapy with stem-cell support [32,33], which is why most current high-dose therapy protocols include chest wall irradiation.

Resolution of questions about the usefulness of chest wall irradiation will come about only through continued clinical research. It is time to initiate a new post-mastectomy chest wall trial in North America. Such a study should incorporate high-quality systemic adjuvant chemotherapy and sophisticated radiotherapy designed to treat all tissues at risk with a minimum amount of radiation delivered to the heart. This trial should include women with four or more positive nodes, who have a higher risk of local chest wall failure than those with one to three positive nodes. Approximately 20,000 women diagnosed with breast cancer annually in the United States have four or more
positive nodes, so that accruing patients to such a trial should not be a problem. The trial should be large enough to detect a 6% to 7% improvement in survival, similar to that seen in the Danish study. Without sufficient clinical trial data from the modern era, such as would be obtained from such a study, we will endlessly debate the role of chest wall irradiation following mastectomy. Discussions are underway with the major cooperative trials groups regarding their willingness to undertake such a study.

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