Controversies Regarding the Use of Radiation After Mastectomy in Breast Cancer

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After completing this course, the reader will be able to:

1. Explain the potential benefits of delivering radiation after mastectomy for patients with breast cancer.
2. Provide a list of appropriate indications for selecting which patients would benefit from radiation after mastectomy and chemotherapy.
3. Appreciate how radiation can potentially cause cardiovascular injuries and understand the importance of radiation technique in minimizing the risk for such injuries.
4. Appreciate how immediate breast reconstruction can affect the delivery of postmastectomy radiation.

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Abstract

Despite years of clinical study, there are still many unanswered questions regarding postmastectomy radiation. It is clear that radiation therapy plays a critical role in the multidisciplinary management of patients with locally advanced or inflammatory breast cancer. It is also accepted that postmastectomy radiation is not required for most women with noninvasive disease or stage I disease. Randomized clinical trials studying radiation treatments for women with stage II or III breast cancer have shown that the addition of radiation after mastectomy can reduce local-regional recurrence rates, which then improves survival. However, other data have indicated that the risk of local-regional recurrence after mastectomy and chemotherapy is low for patients with small tumors and one to three positive lymph nodes, leading some to question whether postmastectomy radiation is useful for this group. A second controversy regards the sequencing of postmastectomy radiation and breast reconstruction. In this article we discuss these controversies, review the data that are relevant, and provide our institutional approaches to these issues.

INTRODUCTION

Approximately 25 years ago, Gilbert Fletcher and Eleanor Montague, two leading experts in breast cancer radiation treatments, wrote, "there is, perhaps, no more controversial subject in the management of cancer than the use of postoperative irradiation in conjunction with...mastectomy" [1]. It is ironic that nearly 3 decades later this statement remains true. Breast cancer is a common disease, and the strategy of combining radiation with mastectomy has been investigated since the 1950s. Despite this, there is not an accepted standard of care concerning radiation use for a patient treated with a modified radical mastectomy and systemic therapy for stage II or III breast cancer with one to three positive lymph nodes. Some would strongly advocate that such patients receive radiation and cite randomized prospective data that support its use. Others show that the risk of local-regional recurrence (LRR) for such patients is low and argue that the potential toxicities and the costs associated with postmastectomy radiation in these patients may not be warranted.

In this article, we explore the current controversies regarding the use of radiation after mastectomy for breast cancer. Initially, we review data demonstrating that postmastectomy radiation decreases LRR after mastectomy and, correspondingly, improves breast-cancer-specific and overall survival in appropriately selected patients. We also review the potential toxicities associated with radiation after mastectomy. Given these potential benefits and risks, it is critical that appropriate selection criteria are used to determine who should receive treatment. To help clarify these selection criteria, we review data concerning patterns of failure for patients treated with mastectomy and other adjuvant or neoadjuvant chemotherapy. Finally, we discuss the controversy regarding the sequencing of postmastectomy radiation and breast reconstruction surgery.

BENEFITS AND RISKS OF POSTMASTECTOMY RADIATION

Meta-Analyses

Over the past 5 decades, there have been more than 25 randomized prospective clinical trials that have evaluated the benefits of radiation after mastectomy for patients with breast cancer. Given the long period over which this topic has been studied, it is not surprising that there is considerable heterogeneity in the surgical and radiotherapy treatments among these trials. Despite the variability in trial design and...
treatments, a number of groups have performed meta-analyses of the data from these studies. In 1987, Cusik et al. published the first meta-analysis of data from postmastectomy radiation trials and reported that radiation use was associated with a poorer overall survival [2]. However, in a subsequent update of this analysis, postmastectomy radiation was found to decrease the breast cancer death rate but increase the non-breast-cancer death rate [3]. These competing results lead to an equivalent overall survival between the two groups.

A more comprehensive meta-analysis concerning postmastectomy radiation was recently updated by the Early Breast Cancer Trials' Collaborative Group (EBCTCG) [4]. This group analyzed the actual data from over 15,000 patients treated in clinical trials investigating the use of postmastectomy radiation. The data from this analysis showed that postmastectomy radiation reduced isolated LRR rates. For patients with lymph-node-positive disease, the 10-year isolated LRR rate was 9% in the radiation group versus 24% in the no radiation group. This highly significant reduction in isolated LRR was noted both in the trials that included a standard modified radical mastectomy and the trials that allowed mastectomy with axillary sampling. Despite the reduction in isolated LRR, the 20-year overall survival rates between the postmastectomy radiation and mastectomy alone groups were nearly identical (37.1% versus 35.9%, respectively, \( p = 0.06 \)).

The lack of a survival benefit led many to question whether postmastectomy radiation was of value. These data also led some to conclude that LRR was an unlikely source of distant metastases. However, further data provided by the EBCTCG analysis are inconsistent with this paradigm of thought. Similar to the earlier Cusik et al. study, the EBCTCG analysis found that postmastectomy radiation significantly improved breast-cancer-specific survival (20-year rates of 53.4% versus 48.6%, respectively, \( p = 0.0001 \)) [4]. The most logical explanation for this finding is that when radiation substantially lowers LRR rates, the probability of being cured of breast cancer improves. Unfortunately, in the meta-analyses, the improvement in breast cancer deaths was offset by an increase in non-breast-cancer deaths (\( p = 0.0003 \)) [4]. This has been attributed to an association with the radiation treatment techniques used in some of these trials and injury to cardiovascular structures. Indeed, the authors found that cardiovascular deaths were statistically greater in the patients treated with radiation, whereas deaths due to pulmonary toxicity or treatment-related cancers were not statistically different between the two groups [4]. Therefore, it is conceivable that postmastectomy radiation could improve overall survival if new techniques that selectively avoided treating the heart and vasculature were used.

It is important to recognize limitations of meta-analyses when considering the relevancy of these data to modern breast cancer patients. The EBCTCG meta-analyses purposely included all trials. While this has obvious benefits, there are also major shortcomings. Omitting eligibility criteria (patients at low risk for LRR will have less benefit than those at high risk for LRR), radiation dose and fractionation, radiation field design, and quality assurance factors can alter the relative risk and benefits of radiation in a clinical trial. To minimize these confounding effects, Van de Steene et al. recently reanalyzed the EBCTCG data, excluding trials that began before 1970, trials with small sample sizes, trials with relatively poor crude survival rates, and trials that used radiation fractionation schedules that are no longer standard practice [5]. When these less than optimal studies were excluded, postmastectomy radiation significantly improved overall survival, with an odds reduction for death of 12.4%. It should be noted that these data were predominantly powered by the Danish postmastectomy trials, which are discussed later in this paper. It is also important to note that this degree of improvement in overall survival is of the same magnitude as that achieved by the early chemotherapy trials for lymph-node-positive disease [6]. A second meta-analysis focusing on more recent randomized trials also suggested that radiation use improved the overall survival of patients with breast cancer involving stage III disease [7]. This analysis compared the outcome of breast preservation therapy (which included radiation treatment) with modified radical mastectomy and found that breast preservation therapy provided a survival advantage over mastectomy in the trials that did not include postmastectomy radiation (odds ratio favoring breast conservation therapy of 0.69). However, in the trials that compared breast conservation therapy with mastectomy plus postoperative radiation, the two treatments achieved equivalent outcomes. These data again suggest that radiation should be a component of care for women with intermediate-risk breast cancer.

**Modern Postmastectomy Radiation Trials**

It is generally accepted that reproduced large phase III randomized trials provide a higher level of scientific evidence than meta-analyses. A recent study found that meta-analyses frequently fail to accurately predict the results of subsequent large phase III studies [8]. One can argue that such a discrepancy exists with respect to the question of whether postmastectomy radiation improves survival in breast cancer. Subsequent to the initial meta-analyses, 10-year data from three randomized trials investigating postmastectomy radiation provided new insights into the potential benefits of radiation. These studies differed from previous trials in the radiation treatment techniques used and in their use of systemic therapy. The use of chemotherapy is relevant to the relationship between radiation use and survival in that it reduces the competing risk of distant metastatic disease development, making the prevention of LRR more important.

Perhaps the most important of the recent randomized prospective trials is the Danish Breast Cancer Cooperative Group (DBCCG) 82b trial, which randomized 1,708 premenopausal women with stage II or III breast cancer to mastectomy followed by nine cycles of chemotherapy or mastectomy, radiation, and eight cycles of chemotherapy [9]. Radiation therapy consisted of 50 Gy in 25 fractions delivered to the chest wall and draining lymphatics utilizing electron beams in the regions over the heart to minimize dose to the cardiovascular structures. The results showed that patients randomized to radiation had a lower 10-year rate of LRR (13% versus 25%, \( p < 0.001 \), respectively) and an improved 10-year overall survival rate (54% versus 45%, \( p < 0.001 \), respectively). A much smaller study, conducted in Vancouver, Canada, was of a similar design and reported remarkably similar results [10]. In that trial, 318 premenopausal women with lymph-node-positive disease were randomized to receive mastectomy and chemotherapy plus or minus postmastectomy radiation. Patients randomized to receive radiation had a very similar reduction in their 10-year rate of LRR (13% versus 25%, \( p = 0.003 \), respectively) and similar improvement in 10-year overall survival (64% versus 54%, \( p = 0.07 \), respectively). Finally, coincident with the 82b study, the DBCCG conducted a companion trial, 82c, for postmenopausal women [11]. This trial randomized over 1,300 patients to mastectomy and tamoxifen or mastectomy, tamoxifen, and radiation. The magnitude of the benefits for the patients randomized to receive radiation was similar to the two previous studies (10-year LRR rates of 8% versus 35%, \( p < 0.001 \), respectively, and 10-year overall survival rates of 49% versus 36%, \( p = 0.03 \), respectively).

Taken together, these three studies demonstrated that by reducing postmastectomy LRR, radiation could improve overall survival. The data from these studies collectively indicated that a reduction in postmastectomy LRR from 25%–30% to 10% resulted in an absolute survival benefit of 10%, meaning that half of the patients in whom LRR was avoided survived. One important contribution to the improvement in overall survival was the lack of increase in non-breast-cancer deaths. The Danish trials...
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**Indications for Postmastectomy Radiation**

**Mastectomy and Adjuvant Chemotherapy**

It is clear from recent phase III clinical trials that radiation improves the overall survival of women treated with mastectomy and chemotherapy who have a 25%-30% risk of having an LRR. It is more difficult to determine from these studies which subcategories of patients have this degree of LRR risk. Prior to publication of the Danish studies, the standard indications to use postmastectomy radiation were the presence of ≥4 positive lymph nodes or T3 or T4 primary disease. In part, these indications were justified by an investigation of failure patterns in 627 patients treated with mastectomy and chemotherapy without radiation in Eastern Cooperative Oncology Group (ECOG) trials [13]. This study reported that these subgroups of patients had clinically relevant rates of LRR, whereas patients with less than four involved lymph nodes and T1 or T2 primaries had a low risk of LRR. After publication of the Danish 82b trial and the Canadian trial, it became less clear whether postmastectomy radiation should be offered to women with stage II breast cancer with one to three positive lymph nodes. In part, this controversy arose because women with one to three positive lymph nodes made up a large percentage of both study populations. Specifically, in the much larger 82b trial, 63% of the patients had one to three positive lymph nodes [9]. However, many patients in that trial did not undergo a formal level I/II axillary dissection. In the Danish 82b trial, the median number of axillary lymph nodes resected was only seven, with 76% of the patients having less than 10 lymph nodes removed, and 15% having three or fewer lymph nodes removed [9].

The potential consequences of having less than a standard axillary dissection are twofold. First, axillary sampling procedures lead to an underestimation of the true number of positive lymph nodes. It is, therefore, likely that many of the patients reported to have one to three positive lymph nodes in the Danish trial may have had four or more positive lymph nodes if a more extensive surgical procedure had been performed. Secondly, the more limited dissection also increased LRR risk by failing to remove microscopic axillary disease. Indeed, in the patients who did not receive radiation, 45% of all LRR in the Danish study occurred in the axilla [14]. This percentage is significantly higher than the contributions of axillary recurrences to total LRR reported in other series that had standard axillary dissections [15, 16].

To further investigate the risk of LRR for patients treated with mastectomy and chemotherapy, a number of groups recently have again explored failure patterns in women treated without radiation. These data are summarized in Table 1 [15–18]. The axillary surgical procedures in these series were different from the surgery performed in the Danish studies. Specifically, the median numbers of lymph nodes recovered in the ECOG and M.D. Anderson Cancer Center series were 15 and 17, respectively, over twice the median number recovered in the Danish trials [15, 16]. In addition, the patients in many of these series were treated with doxorubicin-based chemotherapy, which has been suggested to have a greater efficacy than newer anthracycline-containing regimens [6]. The average rate of LRR for patients with one to three positive lymph nodes in these series was approximately 12%, which is almost three times less than the LRR rate in the no radiation arm in the Danish trials [9, 11, 15–18]. Correspondingly, as the risk for LRR was significantly less, the expected benefit from postmastectomy radiation is unknown. Hypothetically, if postmastectomy radiation had a similar proportional reduction in LRR and improvement across all disease stages, then a patient with a 10-year risk of LRR of 12% would be expected to have an absolute rate of improvement in LRR of 8% and an absolute survival benefit of 4%. However, it is unknown whether these assumptions are accurate. It is not clear that the proportional benefit of radiation on survival remains constant as the risk of LRR decreases. One potential problem with extrapolating data from one risk group to another is that the potential toxicity of postmastectomy radiation would be expected to be roughly equivalent over all risk groups. Therefore, if radiation caused a small increase in non-breast-cancer deaths, it is likely that some threshold of LRR risk is needed for an increased overall survival.

**Table 1.** Ten-year local regional recurrence rates after mastectomy and systemic treatments

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The M.D. Anderson Cancer Center series in Table 1 provides additional information concerning LRR for patients with stage II breast cancer and one to three positive lymph nodes. An analysis of the data from this subgroup found that the presence of extracapsular extension greater than 2 mm, tumor size over 4 cm, positive or close (2 mm) surgical margins, lymphovascular space invasion, or invasion of the skin, nipple, or pectoralis muscle all were associated with rates of isolated LRR ranging over 25% [16, 19]. The one-treatment-related factor that predicted high rates of LRR in patients with one to three positive lymph nodes was resection of less than 10 lymph nodes [16]. In addition, using a recursive partition analysis, those authors found that the most important predictor of LRR was a 20% or greater lymph node involvement [20]. These data are consistent with the Danish data in that the majority of patients with one to three positive lymph nodes in the Danish trials likely had a 20% or greater lymph node involvement because of the low number of total lymph nodes resected.

Recently, both the American Society for Therapeutic Radiology and Oncology and the American Society of Clinical Oncology have published consensus statements regarding postmastectomy radiation. Both of these statements recommend radiation for women with ≥4 positive lymph nodes or advanced primary disease, and both statements highlight the need for additional prospective data concerning the use of postmastectomy radiation for women with T1 or T2 disease and one to three positive lymph nodes [21, 22].

There is currently an ongoing national Inter-Group trial designed to determine the benefits of postmastectomy radiation for patients with small tumors and one to three positive lymph nodes. The schema of that trial is shown in Figure 1. In that trial, patients with stage II breast cancer with one to three positive lymph nodes are randomized to receive postmastectomy radiation or observation after mastectomy and systemic chemotherapy. Patients must have 10 or more lymph nodes dissected and negative margins. Patients with gross extracapsular extension of disease or stage N2 or N3 disease are excluded. This National Cancer Institute-designated high-priority study addresses a critically important clinical question that affects thousands of breast cancer patients in the U.S.
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Neoadjuvant Chemotherapy and Mastectomy

There are substantially less data to aid in determining which patients treated with neoadjuvant chemotherapy warrant postmastectomy radiation. In addition, determining the appropriate selection criteria is more complicated in this group of patients than in those initially treated with surgery. This is because the majority of patients treated with neoadjuvant chemotherapy have a significant change in their disease resulting from the chemotherapy. Therefore, the pathological factors that historically have been used to identify subgroups of patients with clinically relevant risk of LRR after mastectomy are less certain.

Investigators from M.D. Anderson Cancer Center Breast Cancer Group recently reported a study of LRR patterns in 150 patients treated in neoadjuvant chemotherapy trials who did not receive postmastectomy radiation [23]. This population had relatively advanced disease at diagnosis, with 59% of the patients having clinical T3 or T4 stage, and 70% having clinically suspicious lymphadenopathy. As expected, there was a significant change in disease extent with the chemotherapy treatment. After chemotherapy, the median pathological size of the primary tumor was 2 cm and the median number of positive lymph nodes was one.

In a multivariate analysis, three factors were associated with higher rates of LRR. These were clinical stage IIIb disease or greater (hazard ratio 4.5, p < 0.001), 24 positive lymph nodes (hazard ratio 2.7, p = 0.008), and lack of tamoxifen use (hazard ratio 3.9, p = 0.027) [24]. There was no clear relationship between disease response to chemotherapy and LRR. The 5-year rate of LRR for the 18 patients with a complete pathological response was 19% (95% confidence interval [CI] 6%-48%), with all of the failures in this subgroup occurring in patients with either T3 disease or clinical stage IIIB disease at diagnosis. Another interesting subset of patients in this study was 40 patients with residual tumor sizes >5 cm and one to three positive lymph nodes. In this group, the 5-year LRR rate was 46% (95% CI 24%-76%) for patients with clinical T3 or T4 primary tumors compared with only 4% (95% CI 1%-25%) for patients with clinical T1 or T2 disease (p = 0.002).

Those authors also compared rates of LRR in neoadjuvant chemotherapy patients with those previously reported after mastectomy and adjuvant chemotherapy [24]. Not surprisingly, for any given pathology, the risk of LRR was higher in those treated with neoadjuvant chemotherapy. These data indicate that both pretreatment clinical stage and posttreatment pathological findings should be considered when determining indications for radiation after neoadjuvant chemotherapy and mastectomy.

Figure 2 provides the postmastectomy radiation guidelines used at M.D. Anderson Cancer Center.

Sequencing of Breast Reconstruction and Postmastectomy Radiation

Many women who are treated with mastectomy for breast cancer elect to have an autologous tissue breast reconstruction or implant breast reconstruction. A number of advances in the fields of plastic surgery and surgical oncology have significantly improved the probability of achieving an excellent aesthetic outcome after breast reconstruction surgery. One of these advances has been the increased use of skin-sparing mastectomy with an immediate reconstruction. Immediate reconstruction after mastectomy not only allows patients to have one surgical procedure rather than two but also achieves a superior aesthetic result than a delayed procedure because the inframammary sulcus can be preserved. Unfortunately, the use of postmastectomy radiation also has to be considered in deciding the timing and type of postmastectomy reconstruction for breast cancer patients.

Ideally, decisions concerning the sequencing of breast reconstruction and postmastectomy radiation should be made by a closely coordinated multidisciplinary team whose focus is on avoidance of recurrence, improvement of curability, and maximization of long-term quality of life of the patient. As previously highlighted, postmastectomy radiation has been shown to improve survival for selected breast cancer patients and, for most breast cancer patients, cure of the disease is the highest priority. Therefore, the most important question concerning immediate breast reconstruction is whether the reconstruction can impair the efficacy of postmastectomy radiation. To date, this question has never been directly studied. It is clear that all types of breast reconstruction surgeries do not directly have an adverse affect on radiation (i.e., through a modification of the beam). However, breast reconstruction can substantially affect radiation field design. As discussed above, it is imperative that the entire chest wall is treated with postmastectomy radiation, while dose to the lung and heart is minimized. There are a variety of techniques available to achieve this goal. Unfortunately, some breast reconstruction surgeries significantly distort the chest wall anatomy, make the treatment of the targeted tissues more difficult, and often require an increase in the volume of lung or heart irradiated. Most problematic are the steeply sloping medial and apical contours resulting from inflated tissue expanders.

Investigators from M.D. Anderson Cancer Center Breast Cancer Group recently reported a study of LRR patients with stage II breast cancer with one to three positive lymph nodes. Abbreviations: +LN = positive lymph nodes; H&E = hematoxylin and eosin staining; ECE = extracapsular extension of disease.
Our typical approach for chest wall radiation is to treat the medial chest wall and internal mammary lymph nodes with an anterior electron beam field that is geometrically matched to two photon fields designed to treat the lateral chest wall. An example of these field arrangements on an axial computed tomography slice is shown in Figure 3A. The medial electron field has a rapid dose fall-off after the chest wall/lung interface, which, when combined with the more lateral photon fields, treats a small volume of lung. The flat chest wall surface allows for a relatively precise junction of the fields. An example of these field arrangements in the presence of a tissue expander is shown in Figure 3B. One consequence of the expander is that the junction between the fields occurs over a steeply sloping contour. This makes the geometric match less precise, which can lead to underdosing areas of the chest wall in the area under the field junctions. A second consequence of the sloping contour is that the thickness of the chest wall across the width of the electron field becomes nonuniform. The electron beam dose falls off as a function of tissue thickness, so this nonuniformity can also lead to inhomogeneities of dose within the treatment field.

A second negative consequence of performing an immediate reconstruction when postmastectomy radiation is required concerns the impact radiation can have on the long-term aesthetics of the reconstruction. These negative effects are worse for patients with implant reconstruction than for those with autologous tissue reconstruction. Specifically, for women with implants, radiation can promote significant capsular fibrosis.

Based on these two concerns, our multidisciplinary-determined institutional philosophy is to avoid immediate reconstruction in all patients who have clinical features of disease that predict a high likelihood of requiring postmastectomy radiation. After radiation is completed, we then offer autologous tissue reconstruction. These negative effects are worse for patients with implant reconstruction than for those with autologous tissue reconstruction. Specifically, for women with implants, radiation can promote significant capsular fibrosis.

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