Mounting Evidence for Postmastectomy Locoregional Radiation Therapy

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Postmastectomy locoregional radiation therapy markedly reduces the risk of locoregional recurrence. Several randomized trials, including two recently updated studies with 10- to 15-year follow-up, demonstrate an

Introduction

Breast cancer is the most commonly diagnosed malignancy in women in the United States, accounting for an estimated 176,000 new cases in 1999. Most women present without evidence of distant metastases, and, thus, selection of optimal locoregional treatment is important.

Numerous randomized clinical trials involving several thousand women have demonstrated that breast-conserving therapy with wide excision of the primary tumor and breast irradiation provides long-term survival rates equivalent to those achievable with mastectomy.[1,2] The National Cancer Institute 1995 consensus statement endorsed breast-conserving therapy as appropriate and preferable treatment in most patients with early-stage breast cancer.[3] Nevertheless, most US women with early breast cancer continue to undergo a mastectomy, apparently due to a combination of patient and physician preferences, as well as logistical and access issues.[4]

Among patients who have a mastectomy, the role of postoperative locoregional radiation therapy to the chest wall and draining lymphatics has been very controversial. While numerous studies demonstrate that locoregional radiation improves locoregional control, the data regarding its effects on overall survival are conflicting. Some trials suggest an improvement in overall survival,[5-14] while others do not.[2,15-19]

Some of the conflicting results stem from the fact that certain radiation therapy techniques can increase the risk of cardiac disease.[16,18-22] Thus, some of the radiation-induced reduction in death from breast cancer is negated by an increase in radiation-induced cardiac deaths.[16,22]

Two trials recently updated in The New England Journal of Medicine reported improvements in overall survival with locoregional radiation therapy and have renewed enthusiasm for this approach.[8,11] This article reviews the rationale for locoregional radiation therapy and discusses the results of these two trials, as well their implications for our understanding and treatment of breast cancer.

Rationale for Locoregional Radiation

Locoregional Control

Mastectomy and axillary dissection (usually levels 1 and 2) does not remove all locoregional disease in all patients. The probability of the surgeon not removing all microscopic cancer may be gauged approximately by the rate of locoregional relapse following mastectomy and is strongly related to the degree of axillary nodal involvement.[8,11,23-28] Recurrences in the chest wall or regional nodal sites (axillary apex, supraclavicular nodes, and, less frequently, internal mammary nodes) occur in approximately 5% to 10% of women with negative axillary nodes but increase steeply with the degree of nodal involvement (Figure 1). The data in Figure 1 are compiled from multiple studies published over several decades that used different methods to segregate patients and calculate the locoregional relapse rate. Despite these limitations, an increasing risk of locoregional recurrence is consistently related to the degree of axillary involvement.

Figure 2 illustrates the results from several randomized clinical trials that documented the locoregional failure rates without (x-axis) and with (y-axis) locoregional radiation therapy.[5,8,11,12,29-33] These data are fairly well approximated by the line y = 1/3 x, suggesting that the addition of radiation therapy reduces the locoregional relapse rate by approximately 67%.
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(Figure 1), it has often been recommended that patients receive locoregional radiation therapy to reduce locoregional recurrence if they have four or more positive axillary nodes.[2,25] This may be a logical approach with respect to locoregional recurrence but not with respect to survival.[34]

**Survival**

If patients have residual regional disease after mastectomy, locoregional radiation therapy can increase the cure rate only if no subclinical distant metastases are present (or if present, if they can be sterilized by systemic chemotherapy). The conventional wisdom of the last few decades has been that breast cancer is a systemic disease, that involvement of regional nodes is a sign of distant spread, and, hence, that treatment of locoregional sites will not affect survival. These assumptions clearly are not borne out by the data. Node-positive breast cancer is not always a systemic disease. A significant fraction of patients are cured with local therapy alone, without systemic therapy. As summarized in Figure 3, 30-year data from Memorial Sloan-Kettering Cancer Center show that a fraction of patients with small or large cancers and with negative or multiply-positive axillary lymph nodes can be cured without systemic therapy.[35]

Similar data from Milan are shown in Figure 4. Disease-free and overall survival rates at 10 years are ~ 20% to 50% in patients with involved axillary and/or internal mammary lymph nodes, without systemic therapy.[36]

Much of the focus of breast cancer research over the last few decades has been on systemic therapy, leading to a general belief that local treatment is relatively unimportant. This assertion was supported by several studies in early-stage breast cancer showing that lumpectomy plus breast irradiation resulted in a much improved breast control rate than did lumpectomy alone, without marked differences in survival.[1-3,37] Thus, large differences in breast recurrence rates were not readily translated into differences in survival. However, a recent meta-analysis comparing breast-conserving therapy (lumpectomy plus radiation) with mastectomy suggested that breast conservation (in many respects a more aggressive local therapy than mastectomy) provided a superior survival rate, particularly in node-positive patients.[38] The data suggest that breast cancer is not always a systemic disease, even when regional nodes are involved, and that more aggressive local therapy may improve survival.

**Recent Trials**

Danish Breast Cancer Cooperative Group Trial

Overgaard et al recently published the 10-year update of a trial of 1,473 premenopausal women randomized, following mastectomy, to receive CMF (cyclophosphamide, methotrexate, and fluorouracil) with or without locoregional radiation therapy.[8] All enrolled patients had either positive axillary nodes (90%) and/or a T3 tumor (15%). The 10-year actuarial survival rate was 54% in the irradiated patients vs 45% in those treated with mastectomy plus CMF alone (P = .001; Figure 5). The magnitude of the survival benefit was 12% in patients with T3, N0 disease, 8% in those with one to three positive axillary nodes, and 12% in those with four or more positive nodes (Table 1).

The irradiation technique included tangential treatment of the ipsilateral chest wall and internal mammary nodes, as well as a separate supraclavicular and axillary field. The radiation dose was 50 Gy in 5 weeks. The extent of the axillary surgery done in this study was less than is typically performed in the United States, with a median number of recovered nodes of seven.

British Columbia Trial

Ragaz et al reported 15-year results of 318 premenopausal women randomized to receive CMF with or without locoregional radiation.[11] The 15-year actuarial survival rate was 54% in the irradiated patients vs 46% in those treated with mastectomy plus CMF (P = .07; Figure 6). Only patients with positive nodes were included in this study. (Unlike the Danish trial, the British Columbia trial excluded patients with T3, N0 disease.)

Precise data on subsets of patients were not provided. However, the authors noted that the magnitude of the relative benefit was similar in the different subgroups. Subgroup analysis relating to the end point of metastasis-free survival is shown in Table 1; the magnitude of benefit was the same in patients with one to three positive axillary nodes as in those with four or more positive nodes.

The extent of axillary dissection done in this study (median of 11 nodes recovered) was comparable to that performed in the United States. The radiation technique was similar to that used in the study conducted by Overgaard et al, although the fractionation scheme was somewhat unusual (37.5 Gy in 3 to 4 weeks).
While the recent presentation of these two studies in The New England Journal of Medicine has renewed enthusiasm for postmastectomy radiation, this really is not totally new information. Early results from the study of Overgaard et al were published in 1990 in The International Journal of Radiation Oncology Biology and Physics,[7] and the study of Ragaz et al was presented twice at American Society of Clinical Oncology annual meetings in 1993 and 1996.[9,10]

Discussion

Locoregional Radiation Improves Survival in Node-Positive Patients

The two recently updated trials demonstrate improvements in overall survival with locoregional radiation therapy in patients with node-positive (and T3, N0) breast cancer. These data are supported by the results of other randomized trials, which suggest that locoregional radiation improves overall survival (Table 2).

Study Size

Several of these studies are often characterized as negative. However, all of the trials show trends toward improved overall survival with the addition of locoregional radiation therapy. Since these trials were not large enough to detect clinically meaningful differences in survival, the nonsignificant P values may well relate to their small size, rather than to the absence of a real effect. Figure 7 illustrates the total number of patients needed in a two-arm randomized trial to detect a 5% or 10% difference in outcome, as a function of the survival rate of the control group (for a P value of .05 and power of 80%). Each of the individual points in the figure relates to one of the studies in Table 2. As shown in Figure 7, only the Danish trial had a sufficient number of patients to detect a difference of 10%.[39]

Radiation-Induced Cardiac Disease

Another reason why many of the earlier studies testing locoregional radiation therapy may not have demonstrated an improvement in overall survival is radiation-induced cardiac disease. This is well illustrated by the data from the Stockholm trial (Table 3). Radiation therapy clearly reduces the risk of breast cancer mortality. However, this benefit is partly offset by an excess in cardiac deaths. The excessive deaths are seen only in patients who had a relatively large volume of their heart included within the radiation treatment fields.[22] Furthermore, an analysis performed by Harrigan et al at the Joint Center for Radiation Therapy suggests that the dose of doxorubicin used is also a factor in radiation-associated cardiac disease (Table 4).[40] With modern radiation therapy techniques, much of the heart can be excluded from the radiation field and increased cardiac morbidity presumably avoided, although this remains to be proven prospectively.[41]

Survival Benefit of Locoregional Radiation Relative to Number of Positive Nodes

Most of the patients in the studies summarized in Table 2 had one to three, rather than four, positive axillary nodes. Thus, most of the available survival data supporting postmastectomy locoregional radiation therapy come from patients with one to three positive axillary nodes. For the end point of locoregional control, the benefit of locoregional radiation therapy increases with increasing number of positive axillary nodes (Figure 1 and Figure 2), but this may not be true for the end point of survival.

Subgroup data from the two recently updated trials (Table 1) support the concept that locoregional radiation therapy improves survival in patients with one to three positive axillary nodes. Furthermore, the addition of locoregional radiation therapy in node-negative patients increases disease-free survival and may also provide a small improvement in survival.[6,12,14] On the other hand, one must be careful not to extrapolate too widely, since the toxicity of locoregional radiation therapy likely is relatively independent of the degree of nodal involvement, and, thus, the therapeutic ratio of locoregional radiation may not be favorable in node-negative patients.

CT-Based Radiation Treatment Planning Reduces Morbidity and Mortality

Radiation therapy can be toxic and lethal. Therefore, this therapy needs to be delivered carefully by an experienced team (physicians, dosimetrists/physicists, therapists). Radiation dose to the heart and lungs should be kept to a minimum.

For approximately the last 5 years, we have been using computed tomography (CT)-based treatment planning to help place the radiation therapy field borders on the chest wall. Our goal is to irradiate the target tissues and yet minimize incidental irradiation of nontarget normal tissues (eg, the heart and lungs). This is especially important when irradiating the internal mammary lymph nodes (discussed below). We generally try to include the internal mammary nodes within the tangent fields, as this eliminates the potential problems of matching separate anterior internal mammary node fields to the tangent fields. In most instances, the internal mammary node can be included
within the tangent field with an acceptable amount of lung. In our experience, the incidence of radiation-pneumonitis is low. For left-sided lesions, we generally include the upper half of the ipsilateral internal mammary chain in the tangent fields. The lower internal mammary nodes are often not included, as they lie in the shadow of the heart block that is placed to shield cardiac tissue.[41] An electron field is sometimes added to cover the medial inferior chest and the lower internal mammary nodes. Long-term follow-up will be needed to assess the impact of this approach on the heart.

If a separate internal mammary node field is used, care is taken to match this field to the medial tangent. The anterior internal mammary node field is occasionally angled to be nearly parallel (5° to 10° off) to the medial tangent in order to reduce the cold triangle that may exist with abutting fields.[2]

**What Should Be Irradiated?**

The radiation therapy fields used in the studies described above included the chest wall, ipsilateral supraclavicular, axillary, and internal mammary nodes. Since it is unclear to what degree therapy to any of these subsites contributes to the survival benefit, treatment to all sites should be considered. The axillary dissection performed in many European centers is less aggressive than is typically performed at most US institutions. Thus, we generally do not irradiate the entire axilla since we assume that the surgeon has provided adequate treatment of that site and since the frequency of arm edema might increase. Even when the intention is not to treat the entire axilla, portions of the low axilla are often incidentally included in the tangent fields and the axillary apex is typically included in the supraclavicular field.

Although inclusion of the internal mammary nodes within the radiation therapy fields is technically challenging and likely increases morbidity, we generally do try to treat these nodes. Some studies suggest that treatment of the internal mammary nodes by either surgery[42-44] or radiation[5,12,42,44] reduces the incidence of distant metastases. In particular, the Oslo trial suggested a survival advantage following radiation therapy to the regional nodes without the chest wall.[5]

The likelihood of internal mammary node involvement is related to tumor size and location, patient age, and the degree of axillary node involvement. Veronesi et al reported microscopic findings in over 1,000 patients who had a mastectomy with an internal mammary chain dissection.[45] Data from this series (Table 5) showed a relationship between the frequency of internal mammary node metastases and tumor size, axillary nodal status, and patient age. In a study of 535 patients with involved axillary nodes, Handley related the risk of internal mammary spread to the location of the primary and to axillary nodal status (Table 6 and Figure 7).[46]

**Interaction of Systemic Chemotherapy and Locoregional Radiation**

Many patients who are at high risk of locoregional recurrence harbor occult distant metastases. Without systemic chemotherapy, most of these patients will succumb to distant disease. If the tumor burden is greater locally than in distant sites, however, it is possible that systemic adjuvant treatment may sterilize the latter but not the former. In this scenario, therefore, locoregional radiation therapy added to systemic treatment would improve survival.

As the efficacy of systemic therapy improves, the ability of improvements in locoregional control to translate into improvements in survival will increase. Therefore, advances in systemic therapy will enhance the ability of locoregional radiation therapy to positively affect the outcome of patients with breast cancer. Systemic and local therapies are synergistic, not competitive. This concept is shown schematically in Figure 8.

**Recommendations and Conclusions**

All patients with axillary node-positive breast cancer should be considered for postmastectomy locoregional radiation therapy. This therapy improves locoregional control and, most probably, survival as well. The approximately 5% to 10% improvement in survival is comparable to that provided by adjuvant systemic chemotherapy. Optimal outcome is achieved by a multidisciplinary approach.

**References:**


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