Current Status of Radiation in the Treatment of Breast Cancer

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Radiation therapy in combination with lumpectomy and axillary dissection has remained standard therapy for early-stage disease since the 1970s. Although there has been no definitive trial in patients with ductal carcinoma

Introduction

Radiation therapy continues to have a major therapeutic role in the treatment of breast cancer. Radiation therapy in combination with lumpectomy and axillary dissection has been standard therapy for early-stage disease since the 1970s. There has been increasing interest recently in the use of postmastectomy radiation. A number of areas of controversy surround which patients will benefit from postmastectomy radiation. In addition to the questions about patient selection, the volumes and techniques of radiation continue to be redefined. This review will discuss the current status of radiation in breast cancer, with emphasis on the areas of controversy.

Ductal Carcinoma In Situ

Before the widespread use of screening mammography, ductal carcinoma in situ (DCIS) was an uncommon diagnosis. Rosner, in an American College of Surgeons survey published in 1980, reported that only 2.1% of patients with ductal histology had noninvasive cancer.[1] The age-adjusted incidence of DCIS increased more than 500% between 1973 and 1992.[2]

Treatment Options

Treatment options for DCIS range from mastectomy to excision plus radiation therapy to excision alone. Tamoxifen (Nolvadex) may also play a role in preventing recurrences. Mastectomy is curative in 95% to 100% of patients with DCIS.[3-5] As breast-conserving therapy for early-stage invasive disease became widely accepted, its use began to be investigated in DCIS patients. Table 1 reviews the results of the treatment of DCIS with excision and radiation therapy.[5-10] The follow-up in these series varies, but recurrence rates ranged from 7% to 19%, and approximately 30% to 50% of recurrences were invasive.

No randomized trial has compared mastectomy vs lumpectomy and radiation in DCIS patients, as has been done for invasive disease. The review by Solin et al[9] included 268 DCIS patients from 10 institutions in Europe and the United States, who were followed for a median of 10.3 years (range: 0.9 to 26.8 yr). In this series, the 15-year actuarial rate of local failure was 19% with a 96% cause-specific survival, despite the inclusion of a large number of patients with an unknown margin status. In summary, although there is no definitive trial, the data suggest that excision and radiation therapy is a viable treatment option for patients with DCIS.

A number of investigators have suggested that excision alone may be the most appropriate therapy in selected patients. Silverstein has been a leading proponent of excision alone.[11] He and others developed the Van Nuyes index, which takes into account the size of the tumor, width of the margin, and pathologic classification. Based on their series, patients with a low score have a small chance of developing a recurrence.[11]

In a follow-up publication, it appeared that margin status was highly predictive of recurrence.[12] There are a number of limitations in attempting to generalize single-institution results. These limitations include the retrospective nonrandomized nature of the studies, the ability to reproduce the mammographic and pathologic elements of the evaluations, and the differences in treatment time between patients who had excision and radiation vs radiation alone. These problems have been discussed in detail by Schnitt et al.[13]

Randomized Trials of Radiation Therapy

The most appropriate method for determining the value of radiation therapy in DCIS is a randomized trial. The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a prospective randomized trial in 818 women comparing excision alone vs excision and 50 Gy of radiation.
Negative margins were required. At 90 months of follow-up, the incidence of invasive recurrence decreased from 13.4% to 3.9% with the addition of radiation therapy, and recurrences of DCIS decreased from 13.4% to 8.2%.[8]

Similar results were obtained in a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), in which 1,010 patients were randomized to either excision alone or excision and 50 Gy of radiation. At 4 years, the local relapse-free survival was 84% in the excision-alone arm and 91% in the radiation arm ($P = .005$).[6]

In NSABP trial B-24, 1,804 patients with DCIS were randomized to 20 mg of tamoxifen daily for 5 years or placebo, after lumpectomy and radiation therapy. Initial results at 62 months revealed significant reductions in invasive recurrences (4.1% with tamoxifen, 7.2% without) and a nonsignificant reduction in DCIS recurrences (4.2% with tamoxifen, 6.2% without) with the addition of tamoxifen.[14]

The current status of radiation therapy in the treatment of DCIS should continue to be dominated by the results of well-organized prospective randomized trials. The two large randomized trials reported from the NSABP and EORTC clearly demonstrate the need to add radiation therapy to excision in patients with DCIS. A legitimate argument can be made that there are sufficient data supporting the use of excision alone or combined with tamoxifen in subgroups of patients with a low enough risk of recurrence. This question is being explored in the Radiation Therapy Oncology Group (RTOG) randomized trial 98-04, which is comparing tamoxifen alone vs tamoxifen and radiation in good-risk DCIS patients.

**Breast-Conserving Therapy in Stage I/II Disease**

The local management of early-stage breast cancer has been the subject of much interest over the last 20 years. Treatment options include modified radical mastectomy, with or without reconstruction, or breast-conserving therapy.[15] Six prospective, randomized trials have compared mastectomy with breast-conservation therapy, and all have shown equivalent survival. The results of these trials are summarized in Table 2 and Table 3.[16-21]

**Subgroups Who Do Not Need Radiation**

Investigators have attempted to identify a subgroup of patients with invasive disease who do not need breast irradiation. In NSABP B-06, breast recurrences decreased with the addition of radiation in each tumor size group. In the smallest tumors ($\leq 1.0$ cm), breast recurrences decreased from 21% to 11% ($P = .06$).[22]

The Joint Center for Radiation Therapy at Harvard attempted to identify a subgroup of patients for whom treatment with conservative surgery alone would be appropriate. They performed a prospective single-arm trial. Eligibility for the trial included a tumor size $\leq 2$ cm, negative axillary nodes, no lymphatic vessel invasion, no extensive intraductal component, and microscopic margin of at least 1 cm. With a median follow-up of 66 months, the crude local recurrence rate was 20%.[23]

Given the available data, breast irradiation continues to be standard treatment after conservative surgery in all subgroups of patients.

**Areas of Controversy**

There is general agreement about the appropriateness of breast-conserving therapy in stage I and II disease, but some areas of controversy remain regarding the specifics of radiation. These include the need for a tumor bed boost in patients with negative margins and the exact target volume.

**Tumor Bed Boost:** With the exception of the NSABP trial, all the other randomized trials listed in Table 2 and Table 3 used a boost to the tumor bed. A randomized trial reported by Romestaing et al.[24] in 1997 attempted to define the role of a 10-Gy boost after 50-Gy breast irradiation delivered in 20 fractions over 5 weeks. In this trial, 1,024 women were randomized to receive a boost or no boost after whole breast irradiation. At 5 years, the recurrence rate was 4.5% in patients who did not have a boost vs 3.6% rate in those who received a boost ($P = .044$). There was a higher rate of grade I and II telangiectasia in the boost patients, but no difference in the self-assessment score for the overall cosmetic result. Currently, I incorporate a tumor bed boost in the majority of my breast conservation patients.

**Brachytherapy Options:** After breast-conserving therapy, most recurrences occur in the same quadrant as the initial tumor.[25,26] This has led a number of investigators to consider brachytherapy alone after excision of the primary tumor. If brachytherapy could be substituted for external-beam radiation, it might give patients who are unable to receive daily radiation for 5 to 7 weeks the option of breast-conserving therapy. In addition to the logistical benefits of brachytherapy, there may be a biological advantage to the high central tumor bed dose of radiation.
given with brachytherapy and the ability to complete therapy in a short period of time. Guy’s Hospital in Great Britain conducted a pilot study of low-dose rate iridium (Ir)-192 brachytherapy (ie, a dose of radiation delivered by brachytherapy at a rate of approximately 0.4 to 2 Gy/h) without external-beam radiation. This trial required only grossly negative margins and utilized a radiation dose of 55 Gy delivered over 5½ days. The study found a 15% local recurrence rate, with a 96% rate of excellent/good cosmesis as assessed by patients.[27] Kuske et al reported the results of a prospective phase I/II trial in 51 patients who received both low- and high-dose rate brachytherapy (where high dose rate referred to a dose of radiation delivered at a rate of approximately 0.2 Gy/min). Low and high dose rates were alternated in groups of 10 patients with histologically negative margins. Low-dose rate patients received 45 Gy in 3.5 to 6 days; high-dose rate patients received 32 Gy in 8 fractions over 4 days. A 5.8% grade 3 complication rate was seen, with no local recurrences and a 73% excellent/good cosmesis rate.[28] Investigators from William Beaumont Hospital entered 50 patients with tumors ≤ 3 cm and negative margins into a low-dose rate protocol delivering 50 Gy over 96 hours. No patient developed a recurrence, and the good/excellent cosmesis rate was 98%.[29] A study by Polgar and colleagues also noted excellent control and cosmesis with brachytherapy alone after breast-conserving therapy.[30] These results are being confirmed in a multi-institutional RTOG phase I/II trial. Accrual to this trial is complete, and the results are awaited.

Nodal Irradiation

The management of regional nodes in breast cancer has recently undergone major transitions. In the past, the standard breast-conserving technique was excision of the breast primary and an axillary dissection. At present, a sentinel lymph node biopsy is being used increasingly to stage the clinically negative axilla.[31] A properly performed negative sentinel node biopsy should be treated in the same manner as a negative axillary dissection. If the sentinel node biopsy is positive, the current standard of care is to perform an axillary dissection.[32] Approximately 60% of patients with one to three positive sentinel nodes have no further metastasis at the time of completion dissection.[33] This has led to an American College of Surgeons Oncology Group trial, in which patients with a positive sentinel node are being randomized to axillary dissection vs no further axillary treatment. This trial does not allow axillary-directed radiation (ie, a third radiation field), although the low axilla will be irradiated in the standard breast tangents.[34] The purpose of the study is to determine whether local therapy (ie, axillary dissection) has a therapeutic benefit, and as such, the study would address issues similar to those raised by postmastectomy radiation.

Axillary Radiation vs Axillary Dissection

Axillary radiation is a viable option for patients who fail to undergo sampling of the axilla and may be a future option for patients who have a positive sentinel node but no further dissection. There have been three randomized trials comparing axillary dissection to axillary radiation in node-negative patients. NSABP B-04 randomized clinically node-negative patients to radical mastectomy, total mastectomy without axillary dissection but with regional radiation, or total mastectomy and axillary dissection. A 3.1% axillary recurrence rate was seen in the radiation group vs a 1.4% rate in the radical mastectomy group and a 1.1% rate in the axillary dissection group.[35] The Institute Curie noted a 2.1% recurrence rate in patients receiving radiation vs a 0.9% for those undergoing axillary dissection.[36] A third trial in patients with tumors < 1 cm reported no difference in axillary failures whether surgery or radiation was used to treat the axilla.[37] At present, there are no prospective randomized trials investigating the efficacy of axillary radiation following a positive sentinel node biopsy without a completion dissection. A recent retrospective review from the Joint Center for Radiation Therapy at Harvard attempted to estimate the efficacy of axillary radiation in patients with a positive sentinel node biopsy. In this evaluation, 126 patients (42 of whom had positive axillary dissection) underwent axillary radiation following a limited axillary dissection. A 7.1% rate of regional nodal failure as the site of first failure was noted in the group with positive axillary disease and a limited dissection.[38] Further research is needed to determine the proper treatment of patients with a positive sentinel node and no further axillary surgery. At present, axillary dissection remains standard therapy. When nodal metastases are present, irradiation of regional nodal basins may be indicated in some, if not all, patients. In patients with four or more positive axillary lymph nodes, irradiation of the supraclavicular fossa is probably indicated. This recommendation is based largely on the incidence of locoregional recurrences in patients with four or more involved nodes who were treated with...
mastectomy alone.[39] There are limited data on regional nodal failures in patients treated with breast-conserving therapy. In studies that evaluated nodal recurrence patterns, there is little justification for regional nodal radiation in patients with three or fewer involved nodes if nodal recurrence is utilized as an end point.[40,41]

**Comprehensive Nodal Irradiation**

Recent trials have suggested a survival benefit for comprehensive postmastectomy irradiation that targets the supraclavicular fossa, axilla, and internal mammary region.[42-44] Comprehensive nodal irradiation may be justified if one believes that the survival benefit associated with comprehensive irradiation derives from sterilization of occult locoregional disease not sterilized by chemotherapy, which otherwise serves as a reservoir for distant metastasis. This will be discussed more fully in the "Postmastectomy Irradiation" section that follows.

There should be no biological difference between patients with nodal metastasis treated with breast-conservation therapy and those with similar disease who have undergone mastectomy. Therefore, if comprehensive nodal therapy is justified in the postmastectomy group, it is also justified in patients treated with breast conservation. However, in patients with an intact breast, there are additional technical difficulties—especially in the treatment of the internal mammary region, given the sloping contour of the intact breast.

**Postmastectomy Irradiation**

The use of postmastectomy irradiation has received much attention over the last few years. There is general agreement that certain subsets of patients, despite chemotherapy, are at significant risk for locoregional recurrence, and therefore, radiation is indicated. Recht et al reported on 2,016 patients who were randomized to Eastern Cooperative Oncology Group trials and treated with chemotherapy, with or without tamoxifen, and no radiotherapy. In patients with four or more positive axillary nodes, the 10-year actuarial locoregional recurrence rate was 28.7%, compared to 12.9% in patients with fewer than four positive nodes.[45]

A recent trial reported by Katz et al[39] described 1,805 patients treated at M. D. Anderson Cancer Center between 1975 and 1994 with doxorubicin-based chemotherapy, with or without tamoxifen, and no radiotherapy. In patients with four to nine positive axillary nodes, the 10-year actuarial locoregional recurrence rate was 25%. Tumors > 5 cm with no lymph nodes involved had a locoregional recurrence rate of 29%.

The two most common sites of relapse were the chest wall (68% of relapsed patients) and supraclavicular fossa (41%). In patients with one to three positive lymph nodes, tumors with ≤ 5 cm and ≥ 2 mm of extranodal extension, a 33% 10-year actuarial locoregional recurrence rate was noted, compared to 11% and 9% for patients with no or < 2 mm extranodal extension, respectively.[39] Moreover, a locoregional recurrence rate of 24% was reported with < 10 lymph nodes examined vs 11% with ≥ 10 lymph nodes examined.[39]

**Survival After Postmastectomy Irradiation**

The ability of postmastectomy irradiation to affect survival has remained controversial for many years. In 1994, Cuzick et al reviewed eight trials that had been initiated before 1975 and that randomized patients to radiotherapy. There was no significant difference in the all-cause mortality rate in 10-year survivors. However, an excess of cardiac deaths was apparent in the irradiated group.[46]

In 1997, two randomized trials with long-term follow-up were published that noted significant survival advantages in high-risk premenopausal patients who received comprehensive irradiation in addition to chemotherapy: One was conducted by the Danish Breast Cancer Cooperative Group and the other by investigators from British Columbia.[42,43]

**Danish Breast Cancer Cooperative Group Trial:** In the Danish Breast Cancer Cooperative Group Trial 82b, 1,708 women who were felt to be at high risk (with one or more of the following: involvement of axillary nodes, a tumor size > 5 cm, and invasion of the cancer to skin or pectoral fascia) were randomized to CMF (cyclophosphamide [Cytoxan, Neosar], methotrexate, fluorouracil), with or without radiotherapy. Radiation was delivered to a comprehensive field including the chest wall, supraclavicular fossa, axilla, and internal mammary nodes in the upper four intercostal spaces. The intended dose was 50 Gy in 25 fractions.

Locoregional recurrence rates in light of the number of positive lymph nodes are shown in Table 4. Radiation significantly reduced locoregional recurrences. Table 5 lists the 10-year overall survival with respect to lymph node status. The survival benefit of radiation was seen in all subgroups.[43]

That said, this study has been criticized for the relatively low number of axillary lymph nodes
dissected and the non-doxorubicin-based chemotherapy. The locoregional recurrence rate in the nonirradiated group with one to three positive nodes was 30%, compared to 12.9% in the Recht study[45] and 11% in patients without extranodal extension in the Katz study.[39] A similar benefit for postmastectomy radiation therapy was noted in the Danish Breast Cancer Cooperative Group Trial 82c, in which postmenopausal women received tamoxifen and were randomized to radiotherapy or no radiotherapy.[44]

**British Columbia Trial:** A second study published in 1997 also revealed a survival advantage to postmastectomy radiation. In this study from British Columbia, Canada, 318 premenopausal women with node-positive cancer were randomized to either receive or not receive radiotherapy. After 15 years of follow-up, an 8% survival advantage was seen in the irradiated patients. The same survival advantage was seen in the group of patients with one to three involved lymph nodes as in patients with four or more involved nodes.

Ragaz et al[47] recently updated the results of the British Columbia trial in patients with one to three positive lymph nodes in an analysis of the impact of extensive nodal or extracapsular spread. There was a marked overall survival advantage in patients with extracapsular spread, demonstrated by an overall survival of 39% in the nonirradiated group vs 65% in the irradiated group. This advantage was seen despite a lack of difference in the rate of locoregional control. These results support the hypothesis that the locoregional disease that remains after definitive surgery may be an important source of systemic disease and suggest that locoregional control may not be the key end point in evaluating the role of radiotherapy in breast cancer. Currently, the role of postmastectomy radiation therapy in patients with one to three positive axillary lymph nodes is being evaluated in a randomized Intergroup trial.

**Techniques of Postmastectomy Irradiation**

There is a general consensus that postmastectomy irradiation should encompass the chest wall and supraclavicular regions. In patients with an adequate axillary dissection and no gross extracapsular disease, full axillary irradiation is probably unnecessary. A continuing area of controversy concerns the need for internal mammary irradiation.

In patients with positive axillary lymph nodes, there is a relatively high incidence of internal mammary lymph node metastasis. Veronesi et al reported a 29.1% rate of internal mammary lymph node metastasis in 556 patients with axillary lymph node involvement, who had been treated with extended mastectomy.[48] In general, randomized trials have shown no obvious advantage with surgical treatment of internal mammary nodes,[49,50] although in the Lacour trial, an advantage was seen in T1 and T2 medial tumors with positive axillary lymph nodes.[50] These trials may not have had the statistical power to detect a relatively small survival advantage of 5%.

Arriagada et al in a multivariate analysis of 1,195 patients noted a survival advantage favoring the treatment (with surgery and/or radiation) of the internal mammary chain in patients with positive axillary lymph nodes and medial tumors.[51] Recently published randomized trials noting a benefit to postchemotherapy radiation have also included internal mammary radiation.[42-44] Currently, the European Society for Therapeutic Radiology and Oncology is conducting a phase III randomized trial of the role of internal mammary and medial supraclavicular irradiation in stage I-III breast cancer. A complete discussion of the techniques of radiation is beyond the scope of this review. In general, however, a few topics deserve comment. If comprehensive regional radiation is delivered, techniques to minimize long-term morbidity are imperative in order to maximize the therapeutic ratio of radiation. I generally deliver comprehensive radiotherapy using three-dimensional computed tomography planning in a technique similar to that described by Marks et al.[52] Figure 1 depicts images from the virtual simulation of a patient with a modified wide tangent designed to irradiate the upper internal mammary lymph nodes.

**Conclusions**

Radiation therapy continues to play a major role in the treatment of breast cancer. A number of issues still need to be addressed. Unresolved questions include:
- Is there a group of patients with ductal carcinoma in situ in whom radiation after excision is not indicated?
- Can brachytherapy alone be used in selected early-stage breast cancer patients being treated with breast-conservation therapy?
- Is postmastectomy radiation indicated in all patients with positive axillary lymph nodes?
- Is internal mammary irradiation necessary in any group of patients?

A number of clinical trials are attempting to answer these questions. Until the results of these trials...
are available, individual management of patients should involve a careful review of the patient’s clinical status and a thorough discussion with the patient. The placement of patients into clinical trials should remain a priority.

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