Conservation Therapy of the Breast: Optimizing Long-term Results

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Most patients presenting with localized breast cancer can be managed safely and effectively with breast conservation therapy.

**Background:** Radiation therapy is a key component of breast conservation therapy for breast cancer. There is great interest in safety and long-term outcome issues for this still underutilized approach.

**Methods:** The author reviews a series of factors that may affect the end results of conservation therapy and highlights those that are likely to be of clinical significance.

**Results:** Daily dose fractions are usually less than 2 Gy and a homogeneous whole-breast dose is used. Care is needed with patients with collagen vascular diseases, large breasts, breast trauma, and prior infections, but these factors are not absolute contraindications to breast conservation therapy. Acute skin reactions are not predictive of long-term complications.

**Conclusions:** With adherence to proper surgical and radiation techniques, most patients presenting with localized breast cancer can be managed safely and effectively with breast conservation.

**Introduction**

Breast conservation therapy has been an option for the treatment of mammary carcinoma for over 40 years, and favorable results have been reported in Europe, Canada, and the United States. The intent of breast conservation therapy is to achieve acceptable cosmetic results as well as a high degree of local cancer control that is comparable to complete removal of the breast. While the safety and efficacy of breast conservation as a local treatment have been widely reported, less attention has been placed on the associated goals of treatment concerning cosmetic results and quality of life for women who receive breast conservation treatment. This report focuses on indications for breast-conserving therapy and the treatment techniques used to maximize good cosmetic results while minimizing soft-tissue damage to the breast and surrounding tissues.

**Patient Selection**

Although a National Cancer Institute panel in 1990 recommended breast conservation therapy for early breast cancer as "an appropriate therapy for the majority of women with stage 1 and stage 2 breast cancer," it is not the most common form of local treatment in the United States. Nationwide, only 30% to 35% of patients select breast conservation as treatment for their breast cancer, and regional rates are as low as 20%. Important considerations for the patient and the surgeon in the decision-making process include the expected cosmetic result, the short- and long-term side effects of radiation, and the need for follow-up with physical examinations and mammograms after treatment.

The ability to obtain clear surgical margins and the tumor pathologic characteristics are important considerations in patient selection for breast conservation. Complete tumor removal documented by clear surgical margins has been associated with optimal local cancer control in most reported series. At our institution, adequate surgical margins (defined as negative cytologic touch preparations and permanent histologic sections) have been achieved in over 98% percent of cases in which the breast has been conserved. However, not all cancers are amenable to complete surgical removal, and some pathologic subtypes, such as infiltrating lobular carcinoma, present difficulties in obtaining clear margins and may result in a high incidence of local failure after surgery and irradiation.

In patients with invasive carcinoma, lumpectomies with clear margins have been achieved in 93% of attempted surgeries. Within this group, two adverse pathologic subsets have emerged. The first of these, invasive ductal carcinoma with an extensive intraductal component (EIC), has been well documented in other series. At our institution, approximately 30% of patients with this pathologic subtype are unable to undergo breast conservation due to the lack of clear surgical margins. However, our experience suggests that if adequate surgical margins can be achieved, local recurrences after irradiation are acceptably low. Clear surgical margins in invasive lobular carcinoma are difficult to attain. Less than 50% of attempted lumpectomies have resulted in clear margins. The multifocal, single-file pathology of invasive lobular carcinoma makes complete surgical resection difficult in these patients.

Among patients with intraductal cancer, all subtypes have been resected with equal success rates in obtaining clear margins. However, the local recurrence rates for intraductal cancer after excision and radiation appear somewhat higher than those for invasive tumors. Additionally, early analysis of our results suggests that patients...
with multifocal intraductal carcinoma with a component of microinvasion have a high local recurrence rate, with recurrences developing within the first 18 months of follow-up (unpublished data, Cox C, et al, 1997).

**Contraindications to Breast-Conserving Therapy**

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<td>Prior therapeutic irradiation to the breast</td>
<td>First or second trimester pregnancy</td>
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<td>Diffuse, malignant-appearing calcifications</td>
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<td>Tumors that involve greater than one quadrant</td>
<td>Large tumor/breast size ratio</td>
<td>History of connective-tissue disease</td>
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**Breast and Soft-Tissue Reaction**

Short-term reactions to breast irradiation are usually represented by skin syndromes such as edema, erythema, macular-papular rashes, and superficial skin ulcerations. Acute skin reactions often heal rapidly and are not predictive of long-term complications. Chronic complications may involve both the skin and underlying tissues. The most frequent include skin thickening, subcutaneous fibrosis, breast ulcerations, and brachial plexopathy.

The incidence and severity of chronic breast reactions are related to total radiation dose, with whole-breast doses in excess of 55 Gy being associated with a greater than 5% incidence of intense fibrosis. Ulceration is uncommon and is usually associated with focally high radiation doses in excess of 75 Gy. This emphasizes the importance of dose homogeneity in treatment planning. Dose fractionation is also an important consideration for long-term complications. Daily doses in excess of 2 Gy are now rarely used.

Factors other than radiation dose and fractionation also can contribute to an increased incidence of severe skin and soft-tissue reactions. Breast trauma and prior infections predispose to increased fibrosis and ulceration. Connective tissue diseases such as progressive systemic sclerosis (scleroderma), systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome have been associated with increased soft-tissue complications of treatment. A history of these diseases comprises a relative rather than an absolute contraindication to radiation therapy, although the number of such patients who have had severe complications is small. Genetic diseases (eg, the homozygous states of ataxia telangiectasia, Bloom's syndrome, Fanconi's syndrome) are associated with a substantially increased incidence of complications following treatment with radiation therapy. These diseases have defects in the ability to repair radiation-induced double-stranded DNA breaks, which may account for the increased susceptibility to soft-tissue damage. The heterozygous ataxia telangiectasia state is present in 7% to 11% of the adult population. This group also appears to have an increased incidence of complications from therapeutic radiation, ultraviolet light exposure, and perhaps cytotoxic chemotherapy. The extent of this problem is not known, although genetic testing may soon be available to identify affected individuals within the general population.

**Radiation Administration**

The technique used to administer radiation to tissue is believed to influence the functional outcome after treatment. The earliest use of radiation for breast cancer treatment used low-energy radiographs. A single dose was used to effect a brisk erythema in the belief that the skin-killing dose would also lead to tumor destruction. In the late 1920s, technical improvements in the positioning of patients and in the fashioning of tangential breast treatment portals prevented significant doses to the heart and lungs. The development of higher-energy photons, complex dosimetry, and computed tomography (CT)-assisted planning has resulted in further improvements in treatment accuracy that are available in most community settings.

**Treatment of the Breast**

In most circumstances, treatment of the breast alone is effective for local control of carcinoma following tumorectomy. Indications for more extensive treatment of the chest wall and draining lymph nodes include skin involvement, extensive lymph node involvement (ie, more than four positive nodes), and lymphatic space involvement. A 4- to 6-MeV linear accelerator is most commonly used for treatment of the breast alone. Simulation and treatment are achieved with the patient in the recumbent position and the ipsilateral arm extended over the head. This position allows placement of tangential radiation beams that encompass the entire breast without passing through the arm or shoulder.

Treatment of the breast is as homogeneous as possible with the maximum tumor dose being kept within 10% of the overall target volume (whole-breast dose). The need for target-dose homogeneity implies that contours and isodose curves are calculated for each individual. Within the tangential breast portals is a portion of the ipsilateral lung tissue. Between 10% and 20% of the underlying lung tissue receives a full dose. Although radiologic evidence of lung fibrosis is often seen, the incidence of symptomatic lung injury is less than 2%. Left-sided breast tumors present additional problems concerning the underlying heart. CT-assisted planning is essential to establish the geometric relationship between the breast and underlying left ventricle. At our institution, approximately 5% to 10% of underlying heart tissue is encompassed within the tangential treatment portals. With the common use of high-dose doxorubicin and other potentially cardiotoxic drugs, avoiding overirradiation of the heart is an important consideration.

The fractionation and total dosage of radiation for optimal treatment of breast cancer are well established. Cosmetic results are optimized with fraction sizes of 1.8 to 2.0 Gy given daily to total doses of 46 to 50 Gy. The need for a "tumor bed" dose remains controversial. At most centers where breast cancer is treated with breast-conserving techniques, a 10- to 15-Gy boost with electrons is used. Both randomized and retrospective trials suggest a boost is useful in all cases where surgical margins are close or involved. In patients with clear surgical margins of more than 3 to 5 mm, the boost may be omitted with little likelihood of increased local failure.

**Treatment of Draining Lymph Nodes**

In patients at high risk of chest wall and lymph node recurrence, additional soft tissues are incorporated in the treatment portals to improve the likelihood of local control. However, including additional soft tissues increases not only the complexity of treatment, but also the likelihood of eventual complications. In patients with dermal lymphatic involvement or a high degree of lymphatic space invasion, the radiation dose must be effectively brought to the skin surface. This leads to increased acute skin and soft-tissue reactions as well as a higher incidence of chronic fibrosis. Placing a suprACLAVICULAR AND AXILLARY PORTAL increases the amount of lung and nerve tissues within the path of the beam. Moreover, the additional area of the axilla under treatment increases the likelihood of arm edema from between 3%-5% to 15%-20%.

Lastly, the supraclavicular and axillary tissues contain a substantial amount of bone marrow that may be compromised to the point of limiting chemotherapy doses.
Techniques to treat the chest wall and draining lymph nodes must avoid overlapping the tangential beams, minimize doses to soft tissues and viscera, and be accurate and reproducible. Immobilization techniques using foam casting, moldable dressings, and slant boards reproduce positioning to within 1 to 2 cm for daily setups. Field-matching techniques using half-beam blocks and couch angles effectively eliminate overlapping or underdosing.

Treating the internal mammary node chain presents a particular problem. The incidence of internal mammary node positivity is less than 5% in patients with upper-outer quadrant carcinomas with negative lymph nodes. However, in medial carcinomas with positive axillary lymph nodes, internal mammary involvement may reach 40%. Treatment of the chain with an en-face photon field is accurate but is associated with sternal bone marrow depletion and a substantial incidence of esophagitis. The appropriate use of CT scans or lymphoscintigraphy can identify the ipsilateral internal mammary chain nodes, and techniques can be used to incorporate them in the tangential beams.

**Integration of Systemic Therapies With Irradiation**

Approximately 45% of patients with localized invasive breast cancer will receive adjuvant chemotherapy or hormonal therapy. The interdigitation of these systemic medications with local breast irradiation has been the subject of numerous studies attempting to determine the optimal sequencing of drug and irradiation. Strategies for sequencing chemotherapeutic drugs and local irradiation may affect both long-term survival and local control. Data related to effects of sequencing on survival are inconclusive. Two randomized trials show no adverse effect on survival when irradiation precedes chemotherapy. Additionally, in a three-armed trial randomizing (1) chemotherapy followed by irradiation, (2) irradiation followed by chemotherapy, or (3) a sandwich of chemotherapy/irradiation/chemotherapy, the sandwich program exhibited the best overall survival.

Several nonrandomized trials suggest that significant delay in initiating irradiation may result in decreased overall survival, but this trend has not been demonstrated in any of the larger randomized trials. In summary, survival data do not convincingly show decreases in survival when irradiation precedes chemotherapy. Nonetheless, most collaborative group trials are written with up-front chemotherapy under the presumption that delay in administering chemotherapy has adverse prognostic effects on survival.

The effects of sequencing appear to be more conclusive on local control than on survival. Several series document increased local recurrence rates if radiation is delayed for more than six months. In current practice, most doxorubicin-based programs are completed within four to six months, and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) may be sandwiched or given concurrently with irradiation to avoid excessive delay. Little information on appropriate sequencing of tamoxifen and irradiation is available. Because antiestrogens are cytostatic drugs and may move cancer cells into the resting phases of the mitotic cycle, it has been suggested that tamoxifen be delayed until irradiation has been completed. Because irradiation is most effective in treating cells in active portions of the DNA synthesis cycle, many clinicians have followed a program of delaying initiation of tamoxifen until irradiation is complete.

**Skin Care**

During a six-week treatment of radiation to the breast, significant reactions to the breast skin often develop within the second to fifth week, especially for women with fair skin or large breasts. To prevent increased skin reaction, patients are counseled to avoid using heavy moisturizing creams as well as antiperspirants that contain aluminum or magnesium compounds. Most institutions follow a prophylactic skin-care program using a combination ointment that contains aloe, allantoin, or lanolin. If symptomatic erythema or radiation dermatitis occurs, the short-term use of corticosteroid ointments may be used for their anti-inflammatory effect, although an unwanted skin dryness may occur.

Chronic skin edema or erythema is a significant posttreatment problem. After confirming that chronic problems are not related to an infection or cancer recurrence, we have used oral pentoxifylline for several months with some benefit. Several European studies suggest that superoxide dismutase reduces chronic edema and fibrosis in this setting.

**Cosmetic Results**

Several scoring instruments have been used to document the outcomes of cosmesis following breast conservation therapy (Table). Most of these consist of four grades, with grade-1 results being virtually identical to the untreated breast and with results from grades 4 and 5 representing intense fibrosis, ulceration, or skin thickening. In general, 70% to 80% of patients are placed in grade 1 or grade 2. The dominant determinants of cosmetic outcome are the size of the original tumor in relation to the underlying breast and the placement of surgical scars. Connective tissue diseases may be associated with more intense fibrotic reactions, and postoperative wound infections can severely affect the outcome if not treated promptly.

A number of small series have reported on the success of conservation treatment in large-breasted women. Although the relationship of tumor to breast size is most often favorable for these patients, they have a higher incidence of long-term fibrosis and breast-size discrepancy than other patients. Also, a review of 300 patients from our institution showed that the acute side effects of treatment were somewhat worse, with a 20% incidence of superficial skin breakdown. Despite these findings, breast conservation is often the treatment of choice for large-breasted patients due to the morbidity of mastectomy alone or the complexity of mastectomy with reconstruction and contralateral mastectomy.

The cosmetic results of breast implants are often unfavorable in patients treated for breast cancer with conservation methods. Although the acute side effects of treatment are not different than those in other patient groups, the loss of implant mobility over time may be striking. Skin thickness and texture may remain excellent, but subcapsular fibrosis can lead to chronic pain and fixation of the implant. Unfavorable long-term cosmesis occurs in as many as 40% of patients.

**Long-Term Prognosis and Follow-up**

Patients are routinely followed by physical examination and mammogram after breast-conserving therapy. Our group recommends mammography biannually for two years and annually thereafter. The signs and symptoms of recurrence of breast cancer are the same as those in an unirradiated breast. Breast fibrosis in the area of the tumor-bed boost can persist for many months and can be confused with recurrence. In general, however, clinical recurrences have the typical feel and size of new breast cancers. Mammographic signs of recurrence include new cluster calcifications, asymmetric densities, or occasionally increases in the size of a preexisting scar. The natural history of the postirradiation mammogram includes a slow but progressive return to normal degrees of breast fibrosis, skin thickening, and glandular parenchyma.

Most reports of patients treated with breast conservation indicate a median time to recurrence of 40 to 52 months. Although most recurrences develop within five years, a small but constant risk remains for several decades thereafter. In the Harvard series, the risk of recurrence was constant at 2.5% per year from year 2 to
year 6 and then dropped to 1% per year thereafter.\textsuperscript{49} Seventy-five percent of recurrences develop within the tumor bed or its adjacent surgical scar. Interestingly, the recurrence rate in the tumor bed is approximately 2% per year until year 5 and then drops significantly. The recurrence rate outside the immediate tumor bed is negligible until the fifth year, and it then increases to 1% per year thereafter.\textsuperscript{50}

Local recurrence after breast-conserving therapy is most commonly treated with mastectomy or without reconstruction. Patients who undergo reconstruction with an implant have poor cosmetic results and an increased incidence of complications.\textsuperscript{51,52} These complications may be related to loss of skin elasticity due to prior surgery and irradiation. However, to achieve optimal cosmetic results, most patients undergoing reconstruction will receive a tissue transfer procedure such as a transverse rectus abdominis muscle flap.

The prognosis for patients with local recurrence after initial conservative treatment for invasive breast cancer has been reported by multiple groups, with five-year survival statistics ranging from 35% to 81%.\textsuperscript{33-55} The high incidence of subsequent distant metastasis in this group suggests that these patients might benefit from systemic adjuvant therapy. Little information is available on this subject, but prospective trials are being planned to address this issue.

Patients treated for intraductal cancer with breast conservation have an excellent survival prognosis with local recurrence figures of 6% to 10%. However, at least 20% of recurrences have an invasive component of low volume.\textsuperscript{50} Further observation is necessary to determine whether these patients are at substantial risk for systemic cancer spread.

Conclusions

Breast conservation for mammary carcinoma is safe and effective for the majority of women. Natural history studies have identified optimal characteristics of breast cancer patients for this therapy. Techniques to improve complete surgical removal have led to higher complete resection rates and better cosmetics. Radiation techniques to achieve accuracy and minimize tissue complication are now widely available in community settings. Despite these advances, two out of three women opt for mastectomy as primary treatment. Improved patient and physician education may lead to increased rates of breast preservation.

References


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