Local Management of Primary Breast Cancer

William Small, Jr, MD, and Monica Morrow, MD

Patients with primary breast cancer now have the opportunity to choose among various treatment approaches -- breast-conserving therapy, mastectomy alone, or mastectomy with reconstruction.

Background: Various options are available for the local control of cancer in the breast -- mastectomy, conservation therapy, and mastectomy with reconstruction. Methods: To evaluate the benefits and drawbacks of the available management options, the authors combine their extensive experience with a review of the literature on outcomes from these approaches. Results: Conservation therapy provides survival outcomes similar to those from mastectomy. Differences in local recurrence rates can be minimized by close adherence to guidelines for patient selection, operative approach, and radiation technique. Conclusions: The role of the physician in selecting a local therapy for breast cancer has changed from one of informing the patient of the treatment to assessing the presence of medical contraindications to any of the treatments, educating the patients on each treatment approach, providing access to multidisciplinary consultation, and allowing the patient to choose an appropriate treatment approach.

Introduction

The local therapy of breast cancer has been a source of controversy for many years, with changes in the approach to breast cancer reflecting changes in our understanding of the biology of the disease. Since the 1970s, modified radical mastectomy has been the most common operative treatment for patients with invasive breast cancer in the United States. The term modified radical mastectomy encompasses a number of surgical procedures, all of which include complete removal of the breast and some axillary nodes. Although the modified radical mastectomy does not seem to differ significantly from the radical mastectomy, the procedure represents a major departure from the Halstedian principles of en bloc cancer surgery, and its widespread adoption in the 1970s signaled acceptance of the belief that treatment failure after breast cancer surgery was due to the systemic dissemination of tumor cells prior to surgery and not to an inadequate surgical procedure. Some of the same principles that led to the use of modified radical mastectomy contributed to the development of breast-conserving therapy. These included the recognition that adherence to the principles of en bloc cancer surgery failed to cure many patients, the success of moderate-dose radiation therapy (RT) in eliminating microscopic foci of breast cancer after mastectomy, and the increasingly frequent identification of small breast cancers by mammography.

Today, women with stage I and stage II breast cancer are candidates for treatment with modified radical mastectomy, modified radical mastectomy with immediate reconstruction, or breast-conserving therapy (BCT) consisting of lumpectomy, axillary dissection and RT. In addition, the treatment of breast cancer has evolved from being the domain of the surgeon to a collaborative effort among surgeons, radiologists, pathologists, radiation oncologists, reconstructive surgeons, and medical oncologists.

Breast-Conserving Therapy

Six prospective, randomized trials\(^1\)-\(^6\) have compared mastectomy and BCT, and no statistically significant differences in overall or relapse-free survival have been noted in spite of considerable differences among the trials in patient selection, extent of surgery, and technique of radiation (Table 1).

<table>
<thead>
<tr>
<th>Total Number of Patients</th>
<th>Lumpectomy (Yes)</th>
<th>Overall Survival (%) Radiation Mastectomy</th>
<th>Disease-Free Survival (%) Radiation Mastectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B1</td>
<td>2,105</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>NCIC (US)</td>
<td>213</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>Institut Gustav Roussy</td>
<td>179</td>
<td>10</td>
<td>79</td>
</tr>
<tr>
<td>NCIC (Miami)</td>
<td>701</td>
<td>13</td>
<td>71</td>
</tr>
<tr>
<td>EORTC</td>
<td>902</td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>Danish Breast Cancer Group</td>
<td>905</td>
<td>6</td>
<td>79</td>
</tr>
</tbody>
</table>
Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) have been analyzed by intention to treat \( (n=2,105) \), treatment received \( (n=1,851) \), and exclusion of patients from the St. Luc Hospital \( (n=1,529) \). Regardless of the cohort analyzed, there were no significant differences in overall survival, disease-free survival, or survival free of disease at distant sites in patients who underwent total mastectomy and those treated by lumpectomy alone or by lumpectomy plus breast irradiation.\(^1\)

Local recurrence after breast conservation was seen in 3% to 17% of patients and occurred in 2% to 10% of patients following mastectomy (Table 2). Most breast recurrences after BCT are successfully salvaged with mastectomy, with additional local failures reported in approximately 5% of patients.\(^2,7\) A number of large studies from single institutions confirm the results of BCT reported in randomized trials, with survival rates of 59% to 87% at 10 years and breast recurrence rates of 2.5% to 19%.\(^8,13\) As a result of these studies, the appropriateness of BCT as a treatment for breast cancer is not in doubt. More recent trials have been focused on refinements of the procedure and criteria for patients selection.

### Contraindications to Breast-Conserving Therapy

Successful BCT is dependent on minimizing the risk of local recurrence while maintaining a good cosmetic outcome. In 1992, representatives from the American College of Surgeons, the American College of Radiology, the College of American Pathologists, and the Society of Surgical Oncology developed absolute and relative contraindications to BCT (Table 3).\(^14\) These contraindications are currently being revised in light of emerging information. While there is agreement that radiation cannot be safely given to pregnant women or to those who have received prior therapeutic doses of radiation to the breast region, several of the other contraindications deserve further comment.

<table>
<thead>
<tr>
<th>Absolute contraindications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>First or second trimester of pregnancy</td>
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<tr>
<td>Two or more gross tumors in separate quadrants of the breast</td>
</tr>
<tr>
<td>Diffuse, indurated, or malignant appearing microcalcifications</td>
</tr>
<tr>
<td>History of therapeutic irradiation of the breast region</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large tumor-to-breast ratio</td>
</tr>
<tr>
<td>History of collagen vascular (connective tissue) disease</td>
</tr>
<tr>
<td>Large breast size</td>
</tr>
<tr>
<td>Tumor located beneath the nipple</td>
</tr>
</tbody>
</table>

Gross multifocal or multicentric disease is defined as clinical and/or mammographic evidence of more than one area of malignancy in the breast, while pathologic multicentric disease is defined as two or more tumor nodules noted at the time of surgery or by the pathologist. Surprisingly little information is available on recurrence rates in patients with multicentric disease treated with conservative therapy. In a report by Kurtz et al\(^15\) involving 61 patients with two or more macroscopic cancers treated with surgery and radiation, the local recurrence rate was 25%. However, only one local recurrence was noted in 22 patients with negative margins. Leopold and colleagues\(^16\) reviewed the Joint Center for Radiation Therapy experience and found 10 patients treated over a 13-year period who presented with multiple tumors; four of the 10 developed local recurrence. Margins were not routinely evaluated in these patients. In contrast, Hartsell et al\(^17\) reported a local failure rate of 3.7% in 27 patients with two or more nodules of grossly visible cancer treated with BCT. Only four of these patients had grossly multicentric disease noted clinically before surgery, and none recurred. The available information on BCT in patients with multiple primary tumors is limited by small numbers and lack of attention to margins. Although a study of mastectomy specimens in patients with gross multifocal or multicentric disease indicates that a substantial tumor burden may be present throughout the breast in such cases,\(^18\) further information is needed before concluding that all patients with multiple gross primary tumors require mastectomy.

The use of breast conservation therapy in patients with collagen vascular disease has been debated since a report from the M.D. Anderson Cancer Center in 1989 in which exaggerated acute and late radiation reactions (including two cases of necrosis of the chest wall) were observed in three of four women with preexisting collagen vascular disease.\(^19\) Similar problems have been reported from other institutions,\(^20\) but all of these case reports lack information on the number of patients with collagen vascular disease receiving breast irradiation. In an report by Ross et al,\(^21\) 61 patients with collagen vascular disease receiving irradiation for a variety of primary tumors were compared with a control group matched for tumor site, stage, and radiation dose. No significant differences in the incidence of complications in early or late radiation were noted in this study. This is also an area that would benefit from further study.

Large breast size is considered a relative contraindication to BCT, but this is true only if there are insufficient technical resources to immobilize the breast and ensure dose homogeneity. Tumors located immediately beneath the nipple, another relative contraindication, may necessitate removal of the nipple areolar complex, but this does not increase the likelihood of a breast recurrence. Although removal of the nipple areolar complex worsens the cosmetic result, the patient still maintains a sensate breast mound in contrast to mastectomy, where both the nipple and the breast are removed. We do not consider breast size or tumor location as contraindications to BCT.

### Cosmetic Outcome of Breast-Conserving Therapy

A number of large studies which exaggerated acute and late radiation reactions (including two cases of necrosis of the chest wall) were observed in three of four women with preexisting collagen vascular disease.\(^21\) Similar problems have been reported from other institutions,\(^20\) but all of these case reports lack information on the number of patients with collagen vascular disease receiving breast irradiation. In an report by Ross et al,\(^21\) 61 patients with collagen vascular disease receiving irradiation for a variety of primary tumors were compared with a control group matched for tumor site, stage, and radiation dose. No significant differences in the incidence of complications in early or late radiation were noted in this study. This is also an area that would benefit from further study.

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Maintaining a breast that is cosmetically acceptable to the patient is a major goal of BCT. Several factors associated with the patient, the tumor, and treatment can influence the cosmetic result, but the major determinant of cosmetic outcome is the amount of breast tissue that is resected. This is most convincingly demonstrated in the randomized trial from Milan that compares quadrantectomy to lumpectomy. Of 148 patients who participated in a cosmetic evaluation 18 to 24 months after RT, 21% of patients in the quadrantectomy group had a difference in nipple height of greater than 3 cm compared with 7% in the lumpectomy group. Similar differences in the distance from the midline to the nipple and in the inferior profile of the breast were observed. The technique of RT is also important in cosmetic outcome, with significantly greater amounts of retraction and fibrosis seen with whole breast doses above 50 Gy, as well as with high-boost doses. However, in a small series reported by Matory et al., in which patients were evaluated both prior to and following RT, surgery was found to be the main contributor to cosmetic outcome.

The long-term outcome and stability of the cosmetic results after conservative surgery plus RT have been evaluated in a number of studies from the Joint Center for Radiation Therapy. Cosmka results were excellent when the treated and untreated breast were identical, good when minimal treatment effect was apparent, fair when obvious changes due to treatment were present, and poor when severe alterations in the normal breast were evident. In addition, individual elements of cosmetic outcome such as breast edema, retraction, and telangiectasis were assessed. In a series of 593 patients treated between 1968 and 1981, the overall cosmetic result at five years was excellent in 65%, good in 25%, fair in 7%, and poor in 3%. During the first three years after treatment, overall cosmetic results declined, paralleling the development of breast retraction, and then stabilized through seven years of followup. Retraction was the major determinant of cosmetic outcome. Of the 36 patients with fair or poor results at three years, 78% had moderate or severe retraction compared with only 6% of 266 patients with good or excellent scores.

**Local Recurrence**

Recurrent carcinoma in the breast after conservative surgery plus RT occurs in 2.5% to 20% of patients by 10 years after treatment. In contrast to local failure following mastectomy, most of which occurs in the first three years after surgery, the time to local failure after conservative surgery plus RT may be prolonged. Kurtz et al. observed that the actuarial incidence of breast recurrence following treatment increased from 7% at five years to 14% at 10 years and 20% at 20 years. Recurrences at or near the primary tumor site are usually seen within the first 10 years posttreatment, while recurrences elsewhere in the breast occur later. Kurtz et al. also reported that breast recurrences at a distance from the primary tumor, 32% occurred after five years, while 14% occurred during the first five years posttreatment. After five years, the risk of recurrence elsewhere in the treated breast is similar to the risk of developing a contralateral breast carcinoma, thus suggesting that whole breast irradiation, while effective at eradicating microscopic multicentric disease, does not prevent the subsequent development of new carcinomas.

Much attention has been devoted to the identification of factors associated with an increased risk of local recurrence. These factors can be divided into patient characteristics such as age, family history of breast cancer, tumor factors such as size and nodal status, and treatment factors. Young patient age -- variously defined as less than age 40, age 35, or age 30 -- has consistently been found to be associated with an increased risk of local recurrence. Some of this increase in risk is due to an association between young age and pathologic features such as high histologic grade, the absence of estrogen receptors, lymphatic vessel invasion, and the presence of an extensive intraductal component (EIC). However, even after controlling for these factors, young patient age is still associated with an increased risk of breast failure in some studies. Young patient age is also associated with an increased incidence of local recurrence after mastectomy. These findings suggest that while age should not be used as a selection factor for the type of local therapy, it is indicative of a poorer overall prognosis.

A family history of breast cancer has not been shown to increase the risk of local failure after BCT. There is concern that women with genetically transmitted breast cancer may be poor candidates for breast conservation. No definitive studies in women documented to have genetic mutations are available, but Marcus et al. reported a study of mastectomy specimens from women with pedigrees consistent with genetically transmitted cancer. No increase in the incidence of multicentric carcinomas or intraductal carcinoma associated with invasive tumors was identified. Although this is a subject for further study, a pedigree consistent with genetic breast cancer is not a contraindication to BCT at this time.

Tumor factors such as size and nodal status are important predictors of the risk of distant relapse, but they are not major predictors of the risk of breast recurrence. This observation is consistent with the findings of Holland et al. who documented that the extent of residual tumor in the breast was not influenced by tumor size. Histologic tumor type is also not a predictor of breast recurrence. Several studies have demonstrated that local failure rates for women with infiltrating lobular carcinoma are similar to those of women with infiltrating ductal carcinoma.

Early studies in which tumors were grossly excised without attention to the inking of margins suggested that the presence of an EIC in association with the invasive carcinoma increased the risk of local recurrence. More recent studies have indicated that when negative surgical margins are obtained, recurrence rates in these patients are similar to those in patients without an EIC. The presence of an EIC is often an indication that a wider surgical resection is needed to encompass the tumor. Some studies have identified lymphatic vessel invasion as a pathologic factor that predicts for an increased risk of local recurrence after BCT. However, lymphatic vessel invasion is also a risk factor for an increased incidence of local failure after mastectomy.

This information suggests that two types of local recurrence may occur following BCT. The first type is indicative of biologically aggressive carcinoma and is similar in behavior to the local recurrences seen after mastectomy. The second type of local recurrence is a reflection of a heavy tumor burden in the breast, and this type of recurrence is more likely to be affected by alterations in therapy such as wider surgical resections and increased doses of RT. When considering mastectomy to avoid the problem of local recurrence after BCT, it is important to recognize that even in stage I and stage II cancer, mastectomy does not guarantee freedom from local failure. As illustrated in Table 2, the incidence of local failure after conservative surgery plus RT did not differ significantly from the incidence of local failure after mastectomy in five of the six randomized trials in which these treatments were compared.

**Extent of Surgery**

A major issue in BCT involves the amount of normal breast tissue to remove as part of a lumpectomy. Although lower rates of local failure are seen with larger surgical resections, large resections are associated with a significantly poorer cosmetic result. Ideally, the extent of breast resection should be individualized based on the patient’s tumor burden. Magnification mammography improves the preoperative definition of tumor extent, and breast preservation was successfully carried out in 216 patients (97%) selected with this technique. Early reports suggest that magnetic resonance imaging can detect microscopic tumor not seen with conventional imaging methods in 10% to 35% of cases. Margin status and histologic tumor type are other parameters that are useful in determining the appropriate extent of breast resection. In general, the absence of tumor
Radiotherapy Technique

The treatment of the breast following lumpectomy and axillary dissection involves delivering 45 to 50 Gy to the whole breast over approximately five weeks, usually followed by a boost dose to the tumor bed. The use of less than 8 Gy/wk has been associated with increased breast recurrence rates. The total dose necessary in patients with negative margins is unclear. With the exception of the NSABP, all of the randomized trials have employed a boost, and the majority of single institution studies with long-term follow-up have used doses to the tumor bed of at least 60 Gy. The histology of the tumor (ie, EIC [positive]) probably also plays a role in the dosage to the tumor bed that is necessary for local control even when margins are negative. Patients with unknown or positive margins should routinely receive supplemental tumor bed irradiation. Local failure rates of 22% to 30% have been reported when patients with positive margins are treated without a boost to the primary tumor site.

The role of regional nodal irradiation in early breast cancer remains controversial. Failures are infrequent in patients with fewer than four positive lymph nodes, and nodal irradiation is not indicated. Even in patients with more extensive nodal involvement, a clear benefit for nodal irradiation is difficult to demonstrate, and the benefits of nodal irradiation in the presence of extracapsular extension of disease have recently been questioned.

Mastectomy and Immediate Reconstruction

Although mastectomy alone remains the most common treatment for breast cancer, the switch from radical mastectomy to modified radical mastectomy and advances in plastic surgical technique have made immediate reconstruction an option for most patients who undergo mastectomy. Concerns about immediate reconstruction have included the possibility of an increased incidence of local failure, a delay in the diagnosis of local failure, or a delay in the administration of adjuvant therapy due to wound healing problems.

No prospective trials have been conducted that compare mastectomy alone to mastectomy and immediate reconstruction, but the available retrospective data do not support concerns about the incidence or detection of local recurrence in the reconstructed patient. Petit et al compared 146 patients treated with both immediate and delayed silicone-gel implant reconstruction to a control group of patients treated with mastectomy alone. The groups were matched for age, year of diagnosis, stage, histologic tumor type and grade, and nodal status. At 10 years, 8% of the reconstructed patients had experienced local recurrence compared with 15% of the patients having mastectomy alone. In a similar study, 85 patients having immediate reconstruction using a variety of techniques were compared with 85 control subjects undergoing mastectomy alone who were matched for age, stage, nodal involvement, and receptor status. At 30 months, the incidence of local and distant recurrence did not differ between groups.

The effect of reconstruction on the detection of local recurrence was reported in a study by Noone...
and colleagues\textsuperscript{70} in 306 patients followed for a mean of 6.4 years. Local recurrence at the first site of treatment failure occurred in 5.2\% of the group. Fourteen of the 16 recurrences were in the skin or subcutaneous fat, so detection was not affected by the presence of the reconstruction. The authors observed no delay in the administration of chemotherapy in patients having reconstruction, a finding also reported by Eberlein et al.\textsuperscript{71}

In summary, immediate reconstruction has not been shown to alter the outcome of mastectomy or to delay the administration of systemic therapy. Immediate reconstruction has the advantages of avoiding both the need for a second major operative procedure and the psychologic morbidity of the loss of the breast. The two major reconstructive techniques involve the use of implants or the use of myocutaneous tissue flaps to create a new breast mound. The advantages and disadvantages of the techniques are summarized in Table 4. Implant reconstructions are best suited for women with small- to moderate-size breast with minimal ptosis, while flap reconstructions allow more flexibility in the size and shape of the reconstructed breast. In the past, most breast implants were filled with silicone gel. However, following uncontrolled reports suggested an increased incidence of connective tissue disease in women with silicone implants,\textsuperscript{72,73} the Food and Drug Administration declared a moratorium on their use. Since that time, several epidemiologic studies have failed to demonstrate an increased incidence of connective tissue disorders in women with implants compared with matched control populations.\textsuperscript{74,75} Silicone implants are available for use in breast cancer patients, but many patients opt for saline implants or flap reconstructions as a result of the adverse publicity surrounding silicone implants.

\begin{table}
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Type & Advantages & Disadvantages & Complications \\
\hline
Implant & One-stage procedure & Capsular contracture & Implant rupture or leakage \\
& Short operative time & & Poor cosmetic outcome in large breast \\
& Minimal prolongation of & & \\
& hospitalization and recovery & & \\
& Low cost & & \\
\hline
Tissue expander & Short operative time & Multiple physician visits & Implant leakage \\
& Low cost & Rupture of implant & \\
& Hospitalization and & & \\
& recovery not prolonged & & \\
\hline
Latissimus dorsi flap & Reliable flap & & \\
& Autogenous tissue & & \\
& Natural contour & & \\
\hline
Transverse rectus abdominis & Autogenous tissue & Donor site scar & Major complications \\
myocutaneous flap & Natural contour & Moderate prolongation & \\
& Abdominoplasty & Hospitalization and recovery & \\
& & Implant requirement (rarely) & \\
\hline
\end{tabular}
\caption{Types of Reconstruction After Mastectomy}
\end{table}

Regardless of the reconstructive technique chosen, preservation of the skin envelope of the breast will aid the reconstructive surgeon in obtaining symmetry. From an oncologic point of view, the only skin that must be removed as part of mastectomy is the biopsy scar and the nipple areolar complex (Figs 1A and B). Exposure for complete removal of the breast and axillary contents can be obtained by incision rather than excision of skin. Kroll et al\textsuperscript{76} analyzed 87 patients having 100 reconstructions using a skin-sparing technique who were followed for a mean of 23 months. Two patients developed local recurrence, one of which was associated with widespread metastases. This low rate of local failure is consistent with prior observations that the extent of skin removal in patients treated with mastectomy alone is not a major determinant of the risk of chest wall
The only true contraindication to immediate breast reconstruction for stage I and stage II cancer is the presence of comorbid conditions that would make prolongation of the operative procedure unwise. Age, poor prognosis, and the need for chemotherapy are not contraindications to the procedure. In patients with a high likelihood of needing postoperative RT (larger tumors with clinically suspicious nodes), implant reconstructions should be avoided since RT has been observed to increase the risk of both implant loss and capsular contracture.

Selection of an Operative Procedure

In the absence of medical contraindications, the choice of mastectomy alone, mastectomy with reconstruction, or BCT rests with the patient. Several studies indicate that more than 50% of women in the United States continue to be treated with mastectomy. There is little evidence to suggest that patient preference for mastectomy or medical contraindications to breast preservation are responsible for high mastectomy rates. In a study by Morrow et al of 456 unselected patients with ductal carcinoma in situ and clinical stages I and II breast cancer who were evaluated by a multidisciplinary team, medical contraindications to breast preservation were present in only 26% of patients, and 80% of eligible women opted for breast preservation. Foster et al found that 80% of patients with stage I and stage II cancer treated at the University of Vermont between 1989 and 1990 opted for BCT.

Some studies suggest that physician bias, lack of patient education, or a misunderstanding of the contraindications to BCT is responsible for high mastectomy rates. Tarbox et al surveyed 134 general surgeons in Colorado regarding the belief that survival after mastectomy was equal to survival after BCT for T1 cancers. Twenty-two percent of the surgeons surveyed believed that mastectomy was superior, and an additional 34% responded that although the treatments were probably equal, they biased their presentations toward mastectomy. Surgeons in both of these groups performed mastectomy more often than breast preservation. Tate et al studied factors influencing the choice of surgical therapy in a Kentucky community where only 10% to 20% of early-stage breast cancers were treated by breast preservation. The authors state that this article supports a patient bias as a reason for the low rate of BCT in this group of patients. A more detailed analysis of the data presented reveals significant problems with the understanding of contraindications to BCT. Of the 117 reasons cited as medical contraindications to BCT, 50 (43%) are no longer generally considered as valid reasons not to offer BCT (axillary adenopathy, dense fibrocystic disease, large breast size, centrally located tumors, and EIC when negative margins are achieved). Of the 289 medically eligible patients, 82% selected mastectomy. With effective patient education 51% of the reasons cited by patients for selective mastectomy (ie, fear of radiotherapy and fear of cancer recurrence) could be eliminated. This study suggests problems with an understanding of the contraindications to the BCT as well as with patient education.

In considering the choice between mastectomy (either alone or with immediate reconstruction) and BCT, it is important to recognize that no therapy is "right" for all women. Most studies comparing psychologic distress in patients undergoing mastectomy and in those undergoing BCT have found no significant differences.

The role of the physician in selecting a local therapy for breast cancer has changed from one of informing the patient of the treatment to one of assessing the presence of medical contraindications to any of the treatments, educating the patient as to the available treatments and what each entails, and providing access to multidisciplinary consultation and the time needed to make a treatment choice that meets her needs.
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