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# The Surgical Management of Primary Invasive Breast Cancer

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## Introduction

Breast cancer accounts for about 17 percent of all female noncutaneous malignancies, and it is estimated that worldwide in 1994 more than 850,000 new cases of breast cancer were diagnosed and about 250,000 people died. In 1995 in the United States, it is estimated that 183,400 new cases of breast cancer will be diagnosed and 46,240 people will die.[1]

Although these numbers seem staggering, a positive trend toward earlier diagnosis of breast cancer has occurred. About 75 percent of newly diagnosed breast cancers in 1993 were stage I or II, and about two thirds of all breast cancer were node negative.[2] Stage I and II cancers are by convention grouped together as early-stage breast cancer, while in situ cancers are grouped separately.

The treatment of operable primary breast cancer has also undergone a remarkable evolution in the past several decades. The standard operative procedure has changed from the radical mastectomy to the modified radical mastectomy, and the use of breast-conserving treatment is increasing. Radical mastectomy is no longer the only available option for potentially curative treatment of early-stage breast cancer.

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## Survival for Early-Stage Breast Cancer

Survival for patients with early-stage breast cancer treated with mastectomy alone is excellent, but varies by stage and quantitative nodal involvement.[3] A recent study by Rosen et al[4] provided long-term follow-up of patients treated primarily by modified radical mastectomy. Patients with small tumors and no lymph node involvement (stage I, tumor less than 1.0 cm in widest diameter) had a 10-year disease-free survival rate of 91 percent and a 20-year disease-free survival rate of 88 percent. When all patients with stage I lesions were included, the 10-year and 20-year disease-free survival rates were 83 and 79 percent, respectively. Thus, survival for these patients was excellent, and most attrition occurred within the first decade.

Lymph node involvement, however, had a profound impact on survival. Patients with stage IIA cancer (T1N1) with one involved lymph node had a 10-year disease-free survival rate of 71 percent and a 20-year disease-free survival rate of 66 percent. If two to four lymph nodes were involved, 10-year and 20-year disease-free survival rates were 62 and 56 percent, respectively. For patients with more than four involved lymph nodes, 10-year and 20-year disease-free survival rates were 47 and 43 percent, respectively.

The long-term survival rates in the paper by Adair et al[3] reflect the impact of local-regional care alone, primarily with mastectomy, in an era prior to adjuvant systemic therapy. The primary and often only therapy was radical mastectomy.

Similar results with modified radical mastectomy were reported by Rosen et al.[4] Perhaps even better survival will be observed in the era of cytotoxic chemotherapy. Nonetheless, it seems difficult to argue that breast cancer is a systemic disease from inception when most early-stage breast cancers are seemingly cured with local therapy alone.

## Breast-Conserving Treatment

Mastectomy has traditionally been the gold standard in the treatment of operable primary breast cancer and has yielded both excellent local-regional control and overall disease-free survival in most cases. Survival is the same when comparing historic reports of radical mastectomy with modified radical mastectomy. Breast-conserving therapy (combining partial mastectomy, axillary dissection, and radiation therapy) is not a new approach, but has only recently been systematically compared with mastectomy for local control and survival. Results from six randomized, prospective trials (including more than 4,300 women in total) have now demonstrated similar survival when comparing breast-conserving treatment and mastectomy.[5-10]

### Trends in Use

Despite the reports of excellent results, increases in the use of breast-conserving therapy have been somewhat slow. In an article by Osteen et al,[11] large regional differences in the use of breast-conserving therapy were reported. Nattinger et al[12] reviewed the experience of Medicare patients with breast cancer and also noted a remarkable regional variation in the use of breast-conserving treatment for older patients. The level of use of breast-conserving treatment was highest in the Northeast at about 20 percent, lower in the West and Southwest at about 10 to 15 percent, and lowest in the Midwest and South at less than 10 percent. In a review of data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, it was observed that in the short period from 1983 to 1986, the use of breast-conserving treatment increased.[13] The frequency of use for this therapy was similar among racial groups, and there was marked variation in the use of breast-conserving treatment by geographic region. It would seem that the use of breast-conserving treatment is slowly growing in the United States, although marked regional variations still exist.

None of the papers theorize about the reasons for these differences. Possible explanation may include, among others, varied regional treatment preferences among surgeons and patients, varied regional rates of presentation for advanced-stage disease, and lack of facilities in certain regions for radiation therapy.

### Radiation Therapy

Interestingly, only 56.9 to 80.7 percent of patients receiving breast-conserving treatment in the SEER study were reported to have received radiation therapy.[13] This would seemingly contradict the current standard of breast irradiation for all patients with invasive cancer receiving breast-conserving treatment.

A study by Veronesi et al[14] has brought into question the routine use of irradiation for postmenopausal women. In this study, the local recurrence rate in patients aged 55 years and older treated with quandrantectomy alone compared favorably with the same group treated with quandrantectomy and irradiation. However, the results should be viewed with caution as only a small number of patients were included (106 women in the age group) with a short median follow-up (39 months). In addition the quadrantectomy used in Milan is markedly different from the routine lumpectomy used throughout the United States. Thus, standard practice at present still includes radi-

**Table 1**
**Contraindications to Breast-Conserving Treatment**

| Absolute | Relative |
|---|---|
| Multiple ipsilateral lesions | Tumor/breast size ratio |
| Diffuse malignant microcalcifications | Nipple involvement |
| Steroid dependent collagen vascular disease | |
| Pregnancy | Radiation induced |

ation therapy in routine breast-conserving treatment.

### Surgical Approach

The surgical approach for breast-conserving treatment involves a wide local excision of the primary tumor with histologically proven negative margins and an attempt to place the incision so as to avoid unnecessary tunnelling. Hemostasis is meticulous with the intent to minimize hematoma formation, and the tumor site is marked with metallic clips for subsequent radiation therapy boost. Prior to radiation therapy, a mammogram is obtained to assure that all suspicious microcalcifications have been removed. An axillary dissection is done for all infiltrating tumors with a level I and II dissection for smaller tumors (less than 2.0 cm in diameter) with clinically and intraoperatively negative nodes. A clip is placed at the highest level of dissection for subsequent radiation therapy to the axilla if required. A complete axillary dissection is advocated for larger tumors or for any patient with clinically involved lymph nodes.

### Contraindications

There are few absolute or relative contraindications to breast-conserving treatment. The commonly accepted contraindications in stage I and II breast cancer are depicted in the Table and primarily involve multicentricity and tumor size. Steroid-dependent collagen-vascular disease remains an absolute contraindication because of the universally poor cosmetic results after irradiation.

Overall, local control of early-stage breast cancer with breast-conserving treatment is quite good with local recurrence rates in the range of 0.5 to 1.0 percent per year.[8,14-16] Factors thought to contribute to good results include a fastidious surgical approach to the primary tumor and axillary lymph nodes; radiation therapy to the breast with a boost to the primary site; and, perhaps most importantly, appropriate patient selection. Randomized studies have not allowed for patient selection, but analyses of local recurrence have demonstrated important factors that place patients at increased risk.

## Factors Associated with Recurrence

Patient selection has perhaps the largest influence on local-regional recurrence. Although breast-conserving treatment is a safe choice for most patients, there are certain recognized factors associated with increased risk of local recurrence. It is important to determine these factors because local recurrence is a poor prognostic event, and it has been clearly demonstrated that five-year disease-free survival after recurrence in the breast ranges from 50 to 60 percent.[17-21] Interestingly, the number of salvage mastectomies performed has increased in the United States at the same time that the use of breast-conserving treatment has increased.

The knowledge of the factors associated with recurrence has also increased. The most common factors studied are tumor size and histology, age, presence of extensive intraductal component (EIC), margins, lymphatic vessel invasion, and nodal status. Factors that don't appear to be associated with an increased rate of recurrence are the histologic type and grade of the lesion. Lymphatic vessel invasion is not associated with an obvious increased local recurrence rate, although there are series that have linked lymphatic vessel invasion with increased recurrence.

It has been stated that patients with infiltrating lobular carcinoma have an increased rate of local recurrence compared with patients with infiltrating ductal cancer. In several series, however, recurrence rates were similar for ductal and lobular groups.[22-25] This finding may be misleading, though, because negative margins are often not attainable in patients with infiltrating lobular carcinoma because of the diffuse nature of the growth pattern.

### Tumor Size

Two reports have demonstrated that local control is similar for T1 and T2 tumors.[15,26] Kurtz et al[26] reported on 783 patients who received breast-conserving treatment. The local-regional recurrence rate was 13 percent in the T1 group and 12 percent in the T2 group. Veronesi et al[15] quantified the recurrence rates for different tumor sizes. They observed a recurrence rate of 7.5 percent for patients with tumors less than 1 cm in diameter and 7.6 percent for patients with tumors from 1.6 to 2.5 cm in diameter.[15] They concluded that there is no relationship between tumor size and local recurrence.

Veronesi et al[15] also demonstrated that patients with tumors up to 4.5 cm in diameter have the same chance of long-term survival after breast-conserving therapy as patients with smaller tumors. Maximum tumor size for inclusion into the studies was arbitrarily chosen to include patients primarily with early-stage cancer. Patients with large tumors or a large ratio of tumor to breast size were not included.

### Multiple Primary Tumors

The presence of multiple primary cancers has been associated with an increased risk of local recurrence after breast-conserving treatment. Analysis of any individual series is difficult because of the limited number of patients with multiple lesions. Leopold et al[27] reported a recurrence rate of 40 percent for 10 patients with multiple lesions compared with a recurrence rate of 11 percent for 707 patients with one lesion. They concluded that the use of breast-conserving treatment for patients with more than one primary cancer should be considered with caution. In a similar study by Kurtz et al,[28] 15 (25 percent) of 61 patients with multiple tumors had local recurrence, while 56 (11 percent) of 525 patients with a single tumor had local recurrence. In another small series of patients with multiple lesions, the six-year actuarial recurrence rate was 25 percent for patients with multiple lesions and 12 percent for patients with a single lesion.[29] From these studies, it would appear that patients with multiple primary lesions have an increased risk of local-regional recurrence compared with patients with a single lesion.

### Surgical Margins

The influence of surgical margins on local recurrence remains unclear. At least four large, retrospective reviews have demonstrated that involved margins lead to an increased risk of local-regional recurrence.[30-33] On the other hand, several studies have demonstrated no effect.[28,34] Veronesi et al[30] reported that 13 (5.5 percent) of 237 patients with negative margins had a local recurrence, while six (13 percent) of 46 patients with positive margins had a local recurrence.

Several series have looked at the impact of the size of the resection on local recurrence rates. Ghossein et al[31] reported that after tumorectomy, 41 percent of the cases had positive margins and the local recurrence rate was 15 percent. After wide, local excision, 14 percent had positive margins and the local recurrence rate was seven percent. After quadrantectomy, seven percent had positive margins and the local recurrence rate was five percent. Thus, it would seem that larger resections provide more certainty of negative margins and a related decrease in the number of local recurrences.

Vicini et al[32] reported similar results. For EIC-positive patients with T1 tumors, the local recurrence rate was 29 percent for patients receiving a small resection and 10 percent for patients receiving a large resection. For EIC-negative patients with T1 tumors, the local recurrence rate was nine percent in the small resection group and zero percent for larger resections. For EIC-positive patients with T2 lesions, the local recurrence rate was 36 percent for small resections compared with nine percent for large resections.

Solin et al[34] reported on interesting data suggesting that the issue of surgical margins was in fact in part an issue of radiation therapy. In this study 257 patients with negative margins (defined as a greater than 2-mm rim of normal tissue) were treated with 6,000 cGy of radiation, 57 patients with positive margins were treated with 6,500 cGy, 37 patients with a close margin (defined as less than 2 mm) were treated with 6,400 cGy, and 346 patients with unknown margins were treated with 6,240 cGy. Results indicated no significant difference between groups in five-year disease-free survival, overall survival, or actuarial local-regional control.

The use of such boost to the primary site has been accepted as the standard of care at many centers but has never been proven to be useful in a randomized, prospective study. In the retrospective review by Solin et al,[34] it would appear that at least in those patients with involved margins, there may be a role for radiation boost to the primary site.

## Lymph Node Involvement

Conventional wisdom in the 1970s and early 1980s held that patients with clinically involved lymph nodes were better treated with modified radical mastectomy than breast conservation. In fact this view is still quite prevalent although data now suggest that the opposite may be true. The Milan trial[14] demonstrated that in lymph-node-positive patients treated with either quadrantectomy and radiation therapy or Halsted mastectomy, disease-free survival and overall survival were better for patients treated with quadrantectomy and radiation therapy. In addition Haffty et al[35] reported that patients with positive lymph nodes demonstrated a synergistic effect when breast-conserving treatment was combined with adjuvant chemotherapy.

## Age

The effect of age on the risk of recurrence has been a controversial issue. Recht et al[36] reported on 597 stage I and II breast cancer patients. For the 47 patients aged 35 years and younger, the recurrence rate was 26 percent. For the 550 patients older than 35 years, the recurrence was 10 percent. In another study, the 10-year local-regional recurrence rate was 26 percent in patients aged less than 50 years, whereas it was 12 percent in the patients aged 50 years and older.[33]

Kurtz et al[18,37] reported on the influence of age on local-regional recurrence for 496 stage I and II patients. Of the 62 patients younger than 40 years, 13 (21 percent) had local-regional recurrence, while 48 (11 percent) of the 434 patients older than 40 years had local-regional recurrence. In a compilation of their European experience, Kurtz et al[26,33] reported on 1,382 stage I and II breast cancer patients. In this report 41 (19 percent) of 210 patients younger than 40 years had local-regional recurrence, while 106 (nine percent) of the 1,172 patients older than 40 years had local-regional recurrence. Haffty et al[38] reported on similar results, showing that patients younger than 35 years had a statistically significant increased risk of local-regional recurrence.

In an effort to determine why recurrences were more common in younger patients after breast-conserving treatment, Kurtz et al[39] demonstrated that a lymphocytic stroma reaction was more common in younger patients (36 percent versus 20 percent); younger patients more commonly had a high histologic tumor grade (i.e., grade 3) (42 percent versus 28 percent); and the presence of EIC was far more common in younger patients (21 percent versus six percent).

## Extensive Intraductal Component

The presence of extensive intraductal component has been associated with an increased risk of local recurrence. The definition of EIC has evolved in the last decade. It is now commonly accepted to mean that 50 percent of the index lesion is composed of intraductal carcinoma and intraductal carcinoma is present adjacent to the invasive breast cancer.

Recht et al[21] provided the first study defining the increased risk of local-regional recurrence in patients with EIC, reporting on 597 patients with early-stage breast cancer. In the group of 167 patients who were EIC positive, the local-regional recurrence rate was 25 percent. In the group of 430 patients who were EIC negative, the local recurrence rate was five percent. They also reported that although EIC was more common in younger patients (44 percent versus 31 percent), this alone did not account for the difference in recurrence.

Kurtz et al[33] reported on EIC in 496 patients. In the group of 106 EIC-positive patients, the local recurrence rate was 18 percent. In the group of EIC-negative patients, the local recurrence rate was 7.9 percent. Lindley et al[40] reported on 293 patients treated with breast conservation. In the group of EIC-positive patients, the local recurrence rate was 22 percent. In the EIC-negative group, the local recurrence rate was 10 percent.

In an effort to define the biologic significance of EIC, Holland et al[41] compared histologic findings in mastectomy specimens of EIC-positive and EIC-negative patients. For EIC-positive patients, 59 percent had residual carcinoma present farther than 2 cm from the index lesion compared with 29 percent for EIC-negative patients. In addition, 32 percent of the EIC-positive patients had residual carcinoma at a 4-cm distance from the index lesion compared with 12 percent for EIC-negative patients. This difference continued to farther than 6 cm from the index lesion, where 21 percent of EIC-positive patients had residual carcinoma compared with eight percent for EIC-negative patients.

An interesting corollary can be derived from the study by Vicini et al[32] where they compared local recurrence rates for T1 and T2 lesions depending on the size of the resection and the EIC status. For T1 tumors, EIC-positive patients with small resections had a local recurrence rate of 29 percent compared with 10 percent for EIC-negative patients. For T2 lesions, EIC-positive patients with small resections had a local recurrence rate of 36 percent, but if a large resection was done, the local recurrence rate was nine percent. It therefore is tempting to theorize about a relationship between EIC and margins.

### Systemic Therapy

Finally, interesting information is accumulating about the impact of systemic therapy on local-regional recurrence for patients receiving breast-conserving treatment.[42] Adjuvant systemic therapy has been associated with improved local control. Perhaps in the future an additional indication for the use of systemic adjuvant therapy may be to decrease local recurrence in patients with increased risk of recurrence.

### Patient Selection

Patient selection plays a pivotal role in obtaining excellent local-regional control. Although most early-stage breast cancers have equal opportunity for cure with either mastectomy or breast-conserving treatment, it seems at present that a certain minority are better served with mastectomy.

*There are few absolute or relative contraindications to breast-conserving treatment.*

While survival is about equal for either option, there are certain risks and benefits particular to each. The disadvantage of a mastectomy is the loss of the breast, leading to all of the accompanying difficult psychosocial issues. The advantage is that because the breast is removed, a second primary breast cancer cannot develop. In addition, radiation therapy is rarely required after a mastectomy for early-stage cancer.

Breast-conserving treatment saves the breast, but the patient might develop an additional ipsilateral breast cancer—either recurrence of the prior lesion or development of a new primary. Just as survival for the two options is about equal, so is the psychologic adjustment. A review of the impact of these two therapies by Kiebert et al[43] reports that there are no substantial differences in all aspects of lifestyle adjustments comparing the two modalities.

## Axillary Lymph Nodes

Clinical evaluation of axillary nodal involvement is notoriously inaccurate. Other modalities, such as mammography, sonography, computed tomography, and magnetic resonance imaging, have been equally disappointing for preoperative assessment of nodal involvement.[44-51] CT examination has been done with a positive predictive value of 89 percent, a sensitivity of 50 percent, and a specificity of 75 percent.[46] Limited data from studies of the use of positron-emission tomography, vital staining of sentinel nodes, and radioimmune-guided surgery are encouraging. In the future these modalities may have a profound impact on improving the assessment of axillary nodal involvement in breast cancer.

Survival for primary breast cancer is directly related to the size of the lesion and the involvement of axillary lymph nodes.[52] A clear linear relationship between tumor size and nodal involvement has been established. Nonetheless, even a stage T1A lesion is associated with about a 10 to 15 percent risk of axillary nodal disease.[44,53,54] A recent review of stage T1A cancers demonstrated a negligible level of nodal involvement, but this study was in a small number of patients and contradicts most available information.[44]

About 40 percent of patients with invasive breast cancer have involved lymph nodes. The distribution of axillary lymph nodes is arbitrarily divided into three levels designated I, II, and III. About 40 to 50 percent of the axillary lymph nodes are in level I, about 40 percent are in level II, and the remainder are in level III.[55] Distribution of axillary metastases follows a similar distribution with level I nodes more commonly involved than levels II or III.[54,56-58] Skip metastasis involving nodal disease of level III without involvement of level I or II is an uncommon event and occurs in about one to four percent of cases.

A mathematical model of complete axillary dissections has demonstrated that removal of 10 to 11 lymph nodes for a T1 lesion provides a predictive value of 93 percent that all remaining lymph nodes are negative.[55] Removal of additional nodes increases this predictive value, thus forming the basis for the recommendation that level I and II nodes be removed in the clinically and intraoperatively negative axilla.

Axillary lymph node dissection aids in diagnosis, prognosis, and therapy.[59] In a completely dissected axilla, axillary recurrence is in the range of zero to one percent. In comparison, recurrence rates for undissected axilla range from 20 to 40 percent. It would therefore seem that axillary dissection is a very effective means of controlling axillary nodal disease.

Surgery remains the only proven modality for evaluation and treatment of the axilla. At present surgery yields significant information not otherwise obtainable about nodal involvement. For example, surgery has a significant impact on recommendations for adjuvant therapy, affords excellent local control of the axilla, and has been proven to have a survival benefit.[60,61] At present no other modality achieves all of these goals. Primary radiation therapy to the axilla may in the future be proven to provide long-term local control, but to date limited short-term results have been reported.[62]

A randomized, prospective study has demonstrated that axillary dissection provides a survival benefit.[60] In patients randomized to dissection, less axillary recurrences, visceral metastases, and supraclavicular metastases were noted. A retrospective analysis correlated improved survival with increased extent of the axillary dissection.[63]

Axillary recurrence is a poor prognostic event.[63,64] Most patients with a first site of recurrence in the axilla die of their disease.[63,64] Although axillary recurrence occurred much less frequently in the National Surgical Adjuvant Breast and Bowel project than predicted, this in fact may be a statistical error due to an inappropriately small sample size.[65] Axillary recurrence occurred quickly in 18 to 21 percent of patients randomized to no axillary treatment (median time to recurrence 14 months) and was associated with a poor overall prognosis.[64]

The morbidity of axillary dissection remains one of the most important symptomatic long-term sequelae in the treatment of breast cancer. Complications include ipsilateral lymphedema, intercostal brachial neuropathy, and persistent numbness in the upper chest wall and medial aspect of the upper extremity. Lymphedema may be related to the extent of nodal involvement and the extent of surgery at the time of axillary dissection. The combination of axillary surgery and irradiation leads to inordinately high rates of lymphedema.

Axillary dissection would therefore seem to be both a diagnostic and therapeutic procedure. Postoperative care and adjuvant therapy is predicated upon the quantitative lymph node assessment. In addition survival and disease-free survival are impacted by nodal dissection. CA

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