Revised 2006 (Res. 20)*

PRACTICE GUIDELINE FOR BREAST CONSERVATION THERAPY IN THE MANAGEMENT OF INVASIVE BREAST CARCINOMA

PREAMBLE

These guidelines are an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the American College of Radiology cautions against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, an approach that differs from the guidelines, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines. However, a practitioner who employs an approach substantially different from these guidelines is advised to document in the patient record information sufficient to explain the approach taken.

The practice of medicine involves not only the science, but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

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American College of Surgeons
College of American Pathologists
Society of Surgical Oncology

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Board of Chancellors, American College of Radiology

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I. INTRODUCTION

The establishment of standards of care for medical treatment is a process of building consensus by using the best available scientific evidence. For many years, representatives of the American College of Surgeons, the American College of Radiology, and the College of American Pathologists have surveyed practices throughout the United States to document patterns of medical care, track changes in patterns over time, and relate patterns to patient outcomes.

As the treatment of patients with cancer has progressively become multidisciplinary, studies of patterns of care have become more complex. In an attempt to promote better and more consistent care of cancer patients, representatives of the three Colleges, the American Cancer Society, and the Society of Surgical Oncology first met in 1992 to begin the long process of describing standard practice in one specific area, breast conservation treatment.[1] The meetings and the resulting guidelines were considered only a point of departure from which to involve other disciplines within medicine, educate patients, and establish a framework for developing guidelines for the multidisciplinary management of other types of cancer. The guidelines were updated in 1997 and 2001 to reflect changes in clinical practice that occurred in response to new data.

With the advances in knowledge in a variety of fields related to the treatment of early breast cancer, it is appropriate to revise these documents. In the original 1992 document, the focus was on the treatment of invasive carcinoma of the breast. The increased use of and improvements in mammographic technology have resulted in a marked increase in the diagnosis of ductal carcinoma in-situ (DCIS). A body of knowledge has been developed on DCIS that necessitates a separate treatment

[1]Breast conservation treatment is defined as the excision of the primary breast tumor and adjacent breast tissue (breast-conserving surgery) usually followed by irradiation. Breast-conserving surgery also is commonly referred to as lumpectomy, partial mastectomy, or segmental mastectomy.

of this subject. There is a companion document relating to DCIS (Practice Guideline for the Management of Ductal Carcinoma In-Situ of the Breast [DCIS]).

II. REVIEW AND SUMMARY OF THE LITERATURE

Although radical and modified radical mastectomy were the historical mainstays of the treatment of Stage I and II breast cancer for decades and mastectomy continues to be appropriate for some patients, breast conservation treatment (BCT) consisting of breast-conserving surgery (BCS) and radiotherapy (RT) has become the preferred method of treatment for many patients. The results of prospective, randomized trials have demonstrated the equivalence in long-term survival of mastectomy and BCT for appropriately selected patients with early-stage breast cancer.

A. Prospective Randomized Trials of BCS and RT versus Mastectomy

Six modern prospective randomized trials have compared mastectomy with BCS and RT for Stage I and II breast cancer (Table 1-3) [1-9]. Whole breast irradiation with doses of 45-50 Gy was used in all of the trials, and a boost to the primary site was employed in five of the six trials. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, a dose of 50 Gy was delivered to the entire breast without a boost. This trial required histologically negative margins of resection for patients undergoing conservative surgery and radiation. For the remaining five trials, the total dose to the primary site was equal or greater than 60 Gy. The published results of these trials are presented in Tables 2 and 3. With follow-up times of up to 20 years, there were no significant differences in overall or disease-free survival when comparing the two treatments in any of the trials.

In four of the six randomized trials, there was no significant difference in the risk of a recurrence in the treated breast compared with local recurrence involving the chest wall following mastectomy. In the National Cancer Institute (NCI) trial, a higher local failure rate was observed in the breast conservation group. However in this trial, only gross tumor removal was required for study entry without pathologic documentation of negative margins of resection. Similarly in the EORTC (European Organization for Research and Treatment of Cancer) trial, 81% of the patients in the breast-conserving surgery arm had T2 tumors and 48% of the patients had microscopically positive margins.

Local recurrence after BCS and RT may be due to inappropriate patient selection, inadequate surgery or radiation therapy, or biologically aggressive disease. Inadequate surgery may have contributed to the increased risk of breast recurrence in the NCI and the EORTC trials. Overall, in these trials, the incidence of a recurrence in the treated breast ranged from 3% to 20% (Table 3). The majority of failures in the treated breast can be salvaged with mastectomy, and survival following such treatment is approximately 70% at 5 years. As demonstrated in Table 3, primary mastectomy does not guarantee freedom from local recurrence in Stage I and II breast cancer. The incidence of chest wall recurrence following mastectomy ranges from 2% to 14%.

A meta-analysis [19] of prospective randomized trials comparing BCS and RT to mastectomy has demonstrated no survival differences in seven of these trials. Local recurrence was reported in 6.2% of the mastectomy patients and 5.9% of the patients treated with BCT [10].

Studies in the United States suggest that BCT is underutilized [11,12] and that some physicians continue to use inappropriate selection criteria. In a joint study by the American College of Surgeons and the American College of Radiology, 17,931 patients with stages I and II breast cancer were evaluated to determine factors that predicted the use of mastectomy as local therapy [11]. Patients whose tumors had factors associated with a poorer prognosis — such as larger size, the presence of axillary node metastases, and a higher histologic grade — were significantly more likely to undergo mastectomy than patients with more favorable features. The presence of an extensive intraductal component (EIC) in association with an invasive cancer was also a predictor of increased use of mastectomy. In addition, patient factors, such as increasing age, insurance status, geographic location, residence in a low-income area, and lower education levels, were found to predict a higher use of mastectomy.

Studies of the results of second-opinion consultations confirm that many patients who are appropriate candidates for BCT are not being offered the procedure, while standard contraindications are not recognized for others. Clauson et al [13] reported a significant difference in medical opinion regarding appropriate treatment in 20.3% of 231 patients seen for a second opinion on local therapy at a university breast cancer center. In this study, 29% of patients reported that mastectomy was the only therapeutic option which was offered at their initial consultation. Chang et al [14] reported similar findings, with 32 of 75 patients who had been advised to undergo mastectomy found to be appropriate candidates for BCT when seen for a second opinion at a university center.

An important point regarding BCT is that over time the local recurrence rates have declined. There are a number of reasons for this, including better mammographic and pathologic evaluation as part of patient selection. Perhaps the biggest factor, however, is the widespread use of

systemic therapy, which when combined with RT substantially reduces the risk of ipsilateral breast tumor (or local) recurrence (IBTR). This is best illustrated in the 10-year cumulative rates of IBTR in the NSABP trials for node-negative patients [15]. In B-13, the 10-year rate was 15.3% for patients randomized to no chemotherapy and 3.5% for patients randomized to chemotherapy. In B-14, the 10-year rate was 11% for patients randomized to no tamoxifen and 3.6% for patients randomized to tamoxifen. In the more recent trials (B-20, B-23) in which all patients received adjuvant systemic therapy, the 10-year IBTR rates were less than 5% [15].

The randomized trials have also addressed the issue of second malignancy related to radiation. There has been no difference in the incidence of contralateral breast cancer or a second nonbreast cancer malignancy.

B. Prospective Randomized Trials of BCS +/- RT

An unresolved question is whether RT is necessary in all patients with invasive breast cancer after BCS. Fourteen randomized clinical trials with published results (either in abstract or full manuscript) have compared BCS alone to BCS and RT in patients with early-stage breast cancer [16-29]. These trials, summarized in Table 4, vary with regard to patient selection, the details of the surgery and RT, the use of adjuvant systemic therapy, and the length of follow-up. Some of these trials have had relatively short follow-up. The experience in the trials comparing BCS and RT versus mastectomy demonstrated that at least 10 years of follow-up is required since many breast events occur after 5 years. This need for long-term follow-up is best illustrated in the long-term results of NSABP B-06 [4].

Three trials [18,19,29] have compared breast-conserving surgery with and without RT, in the absence of systemic therapy (Tables 4,5). These trials have demonstrated a substantial reduction in local recurrence with RT (about 70%). No consistent subgroup with a low rate of local recurrence in the absence of RT has been identified. In a single-arm prospective study from the Joint Center for Radiation Therapy, patient with pT1N0, extensive intraductal carcinoma (EIC)-negative and lymphvascular space invasion (LVI)-negative invasive ductal carcinoma with negative margins by at least 1 cm to wide excision alone were treated with wide excision alone. With a median follow-up of 86 months, the (crude) local recurrence rate was 23% [30]. Of note, of the 6 patients with a tubular cancer, 3 had a local recurrence. Similar results were seen in a small randomized clinical trial from Finland [29]. In this trial, 152 women age 40 or older with very favorable breast cancer (evident on mammography, T1, node-negative, extensive intraductal component-negative, progesterone receptor-positive, well or moderately differentiated, DNA diploid with S-phase fraction <8 and with margins at least 1 cm) were randomized after "segmental resection" and axillary dissection to receive breast irradiation or not. None of the patients received adjuvant endocrine therapy or chemotherapy. With a mean follow-up time for surviving patients of 6.7 years, the crude rate of local recurrence was 18.1% for patients without RT and 7.5% in the patients with RT.

Based on the results of these prospective studies, it appears that even a highly selected group of breast cancer patients (based on patient and tumor characteristics) has a substantial risk of early local recurrence after treatment with wide excision alone. Newer markers are needed to more reliably identify patients who can be safely treated with wide excision alone. Vihn-Hung et al [31] performed a pooled analysis of 15 published randomized trials involving 9,422 patients who were randomized to either breast-conserving surgery alone or breast-conserving surgery with RT. They found a relative risk of ipsilateral breast recurrence of 3.0 % in patients not receiving adjuvant RT, and this was associated with an 8.6% increase in mortality (95% confidence interval: 1.003-1.175), compared with irradiated patients.

More recent trials have addressed whether systemic therapy can substitute for RT following breast-conserving surgery (Tables 4 and 5). In the NSABP trial B-21 [20], 1,009 women with tumors measuring less than or equal to 1 cm were randomized following breast-conserving surgery to tamoxifen, RT, or the combination. The 8-year cumulative local recurrence rate was 16.5% for tamoxifen alone, 9.3% for RT, and 2.8% for the combination. Hence, tamoxifen was not able to substitute for RT, and the combination of tamoxifen and RT resulted in very low rates of local recurrence. (The results were similar when only those with ER-positive tumors were examined, with an annual hazard rate of local recurrence of 1.68% per year, 0.69% per year, and 0.21% per year respectively, likely reflecting the small number of ER-negative patients in this study.) Survival, however, was not different between the three arms. Two trials have recently been published looking at this question in older patients with ER-positive breast cancer. Breast cancer in older patients is associated with a lower risk of local recurrence, and these patients are also at greater risk of death from competing risks of other illnesses.

The CALGB trial [26] included patients age 70 or older with clinical stage I, ER-positive disease. All patients received 20 mg of tamoxifen daily for 5 years and were randomized to receive breast radiation (45 Gy whole breast followed by a 14 Gy electron beam boost to the lumpectomy site) or no further treatment. With a median follow-up of 5 years, 4% of the women in the tamoxifen alone group experienced a local or regional recurrence compared to 1% in the group that received RT ($p<0.001$). While there were no differences in overall survival

between the two arms, 107 patients died during the study follow-up, but only six from breast cancer.

In the Canadian trial [27], 769 patients over age 50 with T1 or T2 tumors were randomized following breast-conserving surgery to tamoxifen and RT or tamoxifen alone. Women over age 65 were required to have only a clinically negative axilla, whereas younger women were required to have a pathologically negative axilla. The 5-year actuarial local recurrence rate was 7.7% in the tamoxifen group compared to 0.6% in the arm receiving tamoxifen and RT ($p<.001$). In both trials, margins were required to be negative (no tumor at the inked margin), but neither trial compared results by margin status. While there were only a small number of patients followed to 8 years (86 patients at risk), the Canadian trial found that the 8-year rate of local recurrence without RT increased substantially to 17.6% (compared to 3.5% in the arm that received RT), suggesting that tamoxifen merely delayed local recurrence.

Further follow-up is needed to more fully evaluate the results of these trials. However, the use of hormonal therapy alone in older patients (age 70 or older) with a node-negative ER-positive cancer with clearly negative margins seems to be a reasonable option. This is certainly the case in older patients with serious comorbid illnesses. The results may be less applicable to healthy older patients with an anticipated long life expectancy.

C. Accelerated Partial Breast Irradiation

Accelerated partial breast irradiation (APBI) is an alternative radiation therapy (RT) treatment option that has been utilized in highly selected patients treated with BCT for nearly a decade. The primary advantage of this treatment approach is the reduced time required to deliver post-lumpectomy RT (generally from 6.5 weeks to 5 days or less). The most commonly utilized techniques to deliver APBI include catheter based interstitial brachytherapy, balloon brachytherapy catheter, or 3D conformal external beam irradiation [32-35]. Regardless of which technique of APBI is employed, the scientific justification for APBI is that the vast majority of recurrences after standard BCT occur in the vicinity of the tumor bed. As a result, it is believed that limiting RT to a 1-2 cm rim of breast tissue around the lumpectomy cavity may be adequate to eliminate residual disease in the breast after surgery in certain patients. Since the volume of breast tissue that receives a tumoricidal dose of RT is significantly reduced when APBI is utilized, it is possible (radiobiologically) to safely increase the dose per fraction and, as a result, complete adjuvant RT in a significantly shorter period of time.

To date, most of the experience with APBI has been limited to those patients with invasive breast cancer and highly selected tumors. Although 5-year results with APBI have generally been quite good, data are limited and longer-term follow-up is minimal [32]. The most commonly utilized technique of APBI with the longest follow-up has been catheter-based interstitial brachytherapy. More recently, newer techniques that are more patient and physician friendly have been developed, and the interest in APBI has, as a result, increased dramatically [33]. Several phase III trials exploring the efficacy of APBI have recently been started both in the United States and Europe. At the present time, patients with invasive or noninvasive breast cancer undergoing BCT and interested in APBI should be made aware of the data exploring this treatment approach and given the option of participating in these important phase III studies. Recently, the NSABP and RTOG opened a phase III trial (NSABP B-39/RTOG 0413) comparing the efficacy of APBI with standard whole breast RT. Data from this trial will be critical in helping to determine the long-term efficacy of APBI and the patients most suitable for its application.

III. PATIENT SELECTION AND EVALUATION

Because of the potential options for treatment of early-stage breast cancer, careful patient selection and a multidisciplinary approach are necessary. Four critical elements in patient selection for breast conservation treatment are:

- History and physical examination.
- Breast imaging.
- Histological assessment of the resected breast specimen.
- Assessment of the patient's needs and expectations.

A. History and Physical Examination

Much of the information needed to determine a patient’s suitability for breast conservation therapy can be obtained from a detailed history and physical examination. It is important to note that age per se, whether young or old, is not a contraindication to breast conservation. In the elderly, physiologic age and the presence of comorbid conditions should be the primary determinants of local therapy. The elements of the breast history and physical exam are listed in Tables 6 and 7. When evaluating the physical examination, it is important to note that skin, nipple, and breast parenchyma retraction are not signs of locally advanced breast cancer and do not represent contraindications to breast conservation.

B. Imaging Evaluation

Recent preoperative mammographic evaluation (usually within 3 months) is necessary to determine a patient's eligibility for breast conservation treatment. It should be performed with high-quality, dedicated mammographic equipment in a facility certified by the FDA under the Mammography Quality Standards Act.

Mammographic evaluation prior to biopsy or definitive surgery plays an important role in establishing the appropriateness of breast conservation treatment by defining the extent of a patient's disease, the presence or absence of multi-centricity, and other factors that might influence the treatment decision. It is important for evaluating the contralateral breast. Bilateral mammography is required for palpable lesions as well as nonpalpable lesions that can be identified only radiographically. Nonpalpable masses and microcalcifications comprise an increasing percentage of carcinomas treated with breast conservation.

The breast tumor should be measured in at least two dimensions on the mammographic views or from ultrasonography if it is performed. The size of the tumor should be included in the mammographic report. If the tumor is an indistinct or spiculated mass, approximate dimensions can be given from either the mammogram or the sonogram. The skin of the breast in the area of a mass should be evaluated for thickening that might signify tumor involvement. If the mass is associated with microcalcifications, an assessment of the extent of the calcifications within and outside of the mass should be made, including the dimensions of the area in which calcifications are located. If one or more clusters of microcalcifications are the only markers of the tumor, their location and distribution should be described. For evaluation of masses and microcalcifications, specialized views with positioning adapted to the location of the abnormality may be helpful. Magnification mammography and spot compression is important for characterizing microcalcifications and defining the margins of masses. Ipsilateral multifocality or multicentricity may be present and influence the treatment selection. In every instance, when one abnormality is seen, all areas of each breast should be fully evaluated for the presence of additional disease.

Using magnification mammography and ultrasound, patients with tumors suitable for breast conservation can be selected with a high degree of accuracy [36]. Some studies have suggested that magnetic resonance imaging (MRI) is a useful adjunct to mammography and ultrasound for identifying multifocal and multicentric disease [37-39]. The use of intravenous contrast material (gadolinium) with MRI allows for the detection of regions of high vascularity in the breast, which include many, but not all, breast cancers. MRI has been found to be more sensitive than mammography as a screening technique in patients at very high risk for breast cancer development [40]. Unfortunately, many benign lesions also exhibit high contrast uptake and so the number of false positive examinations is high. This and the cost, the lack of standardization of technique, and the difficulty in biopsying lesions seen only on MRI have limited the wide-spread use of MRI in the evaluation of these patients. Currently, there are no data on whether treatment changes that occur in response to the additional lesions seen on MRI will affect local recurrence rates or overall patient survival.

C. Pathological Features Influencing Treatment Choice

A number of pathologic factors have been assessed for their ability to predict an increased risk of recurrence in the treated breast in patients undergoing conservative surgery and radiation. These factors include histologic type and grade, the presence or absence of tumor necrosis, vascular or lymphatic invasion or an inflammatory infiltrate, the presence and extent of ductal carcinoma in-situ (DCIS) in association with an invasive ductal carcinoma, margins of resection, and pathologic nodal status. The presence of vascular or lymphatic invasion, tumor necrosis, and an inflammatory infiltrate has been associated in several, but not all, studies with a somewhat increased risk of breast recurrence [41,44,45]. Some series have also found an increased risk of breast recurrence in patients with high histologic grade tumors compared to those with low-grade tumors [41-44], although this has not been a consistent finding [46]. Histologic subtype other than invasive ductal carcinoma does not appear to be associated with an increased risk of breast recurrence [47-49]. In particular, patients with invasive lobular cancers with or without associated lobular carcinoma in-situ are candidates for conservative surgery and radiation, provided that the tumor is not diffuse in the breast and that complete excision with negative margins can be achieved. Under these circumstances, there has been no increased risk of breast recurrence in patients with invasive lobular carcinomas treated with conservative surgery and radiation [46,47,49-52].

Patients with positive axillary nodes do not have an increased risk of breast recurrence when treated with conservative surgery and radiation [4-6,8, 46,47,53]. This is in contrast to patients undergoing mastectomy where the number of positive axillary nodes correlates with the incidence of chest wall recurrence. The diminished risk of breast recurrence in node-positive patients may be related to the combined effects of chemotherapy and/or tamoxifen with radiation in these patients.

One histopathologic feature that formerly appeared to be associated with a high risk of breast recurrence following conservative surgery and radiation is the presence of an

extensive intraductal component (EIC). This entity was first described by the Joint Center for Radiation Therapy and by definition consists of the simultaneous presence of DCIS comprising 25% or more of the primary invasive tumor and DCIS in the surrounding normal breast tissue. The definition also includes DCIS with focal areas of invasion. Approximately 20% of women with early-stage breast cancer undergoing conservative surgery and radiation for invasive ductal carcinoma have an EIC. EIC is more commonly seen in younger patients than older patients.

Several series have reported an increased risk of breast recurrence in women with EIC-positive tumors. The risk at 10 years has ranged from 22% to 32%. The increased risk of breast recurrence in EIC-positive tumors appears to be related to the presence of a significant residual tumor burden following gross excision. However, a number of more recent reports have confirmed that negative margins of resection diminish the risk of breast recurrence in EIC-positive tumors [54-56]. Therefore, while the presence of an EIC is a pathologic indicator that the disease in the breast may be more extensive than what is clinically appreciated, it does not appear to be an independent risk factor for local recurrence when the margin status is taken into consideration. Patients with EIC-positive tumors in whom the initial margins of resection are positive should undergo re-excision. If the re-excision margins are negative, current information suggests that these patients are appropriate candidates for conservative surgery and radiation. If the re-excision margins remain positive and further re-excision is not possible, mastectomy is the preferred treatment.

In current practice, microscopic margins of resection are the major selection factor for BCT. There are significant technical considerations and limitations in the assessment of margins, and these are discussed elsewhere. There are also variations in the use and definition of a "close margin" with different groups using 1, 2 or 3 mm as the cutoff. In addition, the amount of cancer that is close to the margin appears to be important [57]. Finally, it is important to interpret the margin status in conjunction with the operative findings. For example, a positive deep margin is not significant if the resection was carried down to the pectoral fascia.

Despite these limitations, patients with negative margins of excision (typically defined as the absence of either invasive or ductal in situ disease at an inked surface) have consistently been observed to have low rates of local recurrence after treatment with BCS and RT and patients with positive margins high rates of local recurrence [54,58-66] (Table 8). The JCRT experience demonstrates an 8-year crude recurrence rate of 7% in 298 patients with negative (including close) inked margins of excision treated with 60 Gy or greater to the tumor bed [60]. These data have the advantage that all slides were re-reviewed by study pathologists and provide 8-year crude results with nearly all patients having been followed for at least 8 years. Of note in this series is that patients received radiation therapy soon after surgery; during this time period, patients were not receiving initial systemic therapy. On multivariate analysis, only margin status and the use of systemic therapy were predictive of local recurrence in the final model. Hence, when margins are known, the presence of an EIC did not have independent prognostic value for local recurrence.

The outcome of patients with close margins of resection has been less clear. In part, this reflects variability in the definition of "close margins". In the JCRT experience, among patients who received prompt radiation therapy, no significant difference was seen in recurrence rates between patients with close margins (1 mm) and those with margins greater than 1 mm using similar doses. Some studies, however, have shown a high rate of local recurrence in patients with close margins (Table 8). It seems prudent in patients with close margins to consider other risk factors, such as young age, the extent of disease that is close to the margin, and EIC, in judging the need for re-excision. There is also data to suggest that close margins may be more of a prognostic factor when patients received initial chemotherapy and delayed radiation therapy [67].

D. Pathologic Evaluation

The excised tissue should be submitted for pathology examination with appropriate clinical history and anatomic site specifications including laterality (right or left breast) and quadrant. For wide excisions or segmental breast resections, the surgeon should orient the specimen (e.g., superior, medial, and lateral) for the pathologist with sutures or other markers. Gross examination should document the type of surgical specimen (e.g., excisional biopsy, quadrantectomy), the size of the specimen, the measured size of the tumor, and the proximity of the tumor or biopsy site to the margins of excision. The presence or absence of tumor at the margins of excision is determined by marking them with India ink or another suitable technique.

Frozen section preparation of tissue obtained from wire localization excisional biopsies of nonpalpable lesions or tumors less than 1 cm is strongly discouraged [68]. Small foci of invasive carcinoma or microinvasive disease may be lost or rendered uninterpretable by freezing artifact. In general, frozen sections should be prepared only when there is sufficient tissue that the final diagnosis will not be compromised and when the information is necessary for immediate therapeutic decisions [68].

The use of compression devices for specimen radiography may be necessary to visualize a nonpalpable lesion in the specimen. However, these devices may result in falsely close margins, particularly in specimens consisting predominantly of fat. This is due to the compressibility of fat relative to the tumor, rather than to any alteration of the tumor.

The pathologist includes certain basic data in each surgical pathology consultation report because they are of prognostic importance or are needed for staging or therapy.

Features that should be included in the surgical pathology consultation report for invasive carcinoma include:

- How the specimen was received (e.g., number of pieces, fixative, orientation).
- The laterality and quadrant of the excised tissue and the type of procedure as specified by the surgeon.
- The measured size of the tumor (in three dimensions if possible), with verification by microscopic examination, particularly for pT1 lesions or those associated with an EIC [69-70].
- Histologic type and grade.
- The presence or absence of coexistent DCIS or an EIC.
- The presence or absence of peritumoral vascular or lymphatic invasion.
- The presence or absence of gross or microscopic carcinoma (either invasive carcinoma or DCIS) at the margins of excision. If tumor is not at the margin, the distance of the tumor or biopsy site from the margin should be stated.
- The presence and location of microcalcifications.
- Lymph node status. This should be recorded as the number of lymph nodes found in the specimen and the number of involved nodes, the size of the largest involved node, and the presence or absence of extension beyond the lymph node capsule.

The presence of a focus of tumor measuring 2 mm or less within a lymph node identified by routine histologic examination is defined as a micrometastasis and is classified as pN1mi [71]. The clinical significance of multiple micrometastatic foci is unknown; however, it is recommended that they also be classified as pN1mi until further information becomes available [70].

The significance of individual cells or isolated cellular groups not larger than 0.2 mm, usually found only by immunohistochemistry, either in a lymph node removed by a routine lymph node dissection or in a sentinel node, is unclear. Lymph nodes in this category are classified as pN0(i+) [70]. Because of uncertainty regarding the clinical significance of cells detected by immuno-histochemistry alone, its routine use on sentinel nodes that are normal by hematoxylin and eosin (H&E) staining is not recommended [72,73].

It is important to specify the presence of any special histologic types of invasive breast cancer (e.g., tubular, mucinous, papillary), most of which are considered low-grade. All ordinary invasive carcinomas (ductal, no special type [NST]) should be assigned a histologic grade; some authors recommend grading invasive lobular carcinoma as well. If a specific grading system is used, this should be stated in the pathology report. The most commonly used histologic grading system is the Elston and Ellis modification of the Bloom-Richardson scheme. This system evaluates degree of tubule formation, nuclear grade, and mitotic rate to determine an overall histologic score [74].

The assessment of surgical margins is arguably the most important aspect in the pathologic evaluation of breast tumor excisions in patients being considered for breast conservation. Although the definitions of “positive” and “negative” margins vary among institutions, microscopic margin involvement appears to be associated with an increased risk of local recurrence and, in most cases, indicates a need for further surgery, such as re-excision of the tumor site.

Microscopic confirmation of the presence or absence of regional or distant metastasis must be done when appropriate tissue is submitted for examination. The AJCC/UICC pTNM classification is recommended for appropriate stage grouping.

Determination of estrogen and progesterone receptors (ER and PR) and HER2/neu status is standard for invasive breast carcinomas. ER and PR status are most commonly determined by immunohistochemistry, while HER/2neu status is determined by immunohistochemistry and by fluorescence in situ hybridization (FISH), singly or in combination. The results of ancillary studies such as these are usually reported in an addendum or supplement to the surgical pathology report.

E. Patient Preferences

Perhaps the most difficult aspect of patient evaluation is the assessment of the patient’s needs and expectations regarding breast preservation. The patient and her physician must discuss the benefits and risks of mastectomy compared to breast conservation treatment in her individual case, with thoughtful consideration of each. Each woman must evaluate how her choice of treatment is likely to affect her sense of disease control, self-esteem, sexuality, physical functioning, and overall quality of life.

A number of factors should be considered:

1. Long-term survival.

2. The possibility and consequences of local recurrence.
3. Psychological adjustment (including the fear of cancer recurrence), cosmetic outcome, sexual adaptation, and functional competence.

For most patients, the choice of mastectomy with or without reconstruction or breast conservation treatment does not impact on the likelihood of survival, but it may have a differential effect on the quality of life. Psychological research comparing patient adaptation following mastectomy and breast conservation treatment shows no significant differences in global measures of emotional distress. Research also does not reveal significant changes in sexual behavior and erotic feelings in the treated breast or nipple and areolar complex. However, women whose breasts are preserved have more positive attitudes about their body image and experience fewer changes in their frequency of breast stimulation and feelings of sexual desirability.

F. Absolute and Relative Contraindications

In the selection of patients for breast conservation treatment with radiation, there are some absolute and relative contraindications:

1. Absolute contraindications
   a. Pregnancy is an absolute contraindication to the use of breast irradiation. However, in many cases, it may be possible to perform breast-conserving surgery in the third trimester and treat the patient with irradiation after delivery.
   b. Women with two or more primary tumors in separate quadrants of the breast or with diffuse malignant-appearing microcalcifications are not considered candidates for breast conservation treatment.
   c. A history of prior therapeutic irradiation to the breast region that would require retreatment to an excessively high total radiation dose to a significant volume is another absolute contraindication.
   d. Persistent positive margins after reasonable surgical attempts. The importance of a single focally positive microscopic margin needs further study and may not be an absolute contraindication.
2. Relative contraindications
   a. A history of collagen vascular disease is a relative contraindication to breast conservation treatment because published reports indicate that such patients tolerate irradiation poorly. Most radiation oncologists will not treat patients with scleroderma or active lupus erythematosus, considering it an absolute contraindication. In contrast, rheumatoid arthritis is not a relative or an absolute contraindication.
   b. Tumor size is not an absolute contraindication to breast conservation treatment, although there is little published experience in treating patients with tumor sizes greater than 4 to 5 cm. However, a relative contraindication is the presence of a large tumor in a small breast in which an adequate resection would result in significant cosmetic alteration. In this circumstance, preoperative chemotherapy should be considered.
   c. Breast size can be a relative contraindication. Treatment by irradiation of women with large or pendulous breasts is feasible if reproducibility of patient set-up can be assured and the technical capability exists for ≥6 MV photon beam irradiation to obtain adequate dose homogeneity.

G. Nonmitigating Factors

There are certain clinical and pathologic features that should not prevent patients from being candidates for breast conservation treatment. These features include the presence of clinically suspicious and mobile axillary lymph nodes or microscopic tumor involvement in axillary nodes. In addition, it is important to emphasize that it is feasible to evaluate the breast for local recurrence. The changes associated with recurrence can be detected at an early stage through the use of physical examination and mammography. The delivery of irradiation in this setting does not result in a meaningful risk of second tumors in the treated area or in the untreated breast.

Tumor location is not a factor in treatment choice. Tumors in a superficial subareolar location may occasionally require the resection of the nipple/areolar complex to achieve negative margins, but this does not impact on outcome. Whether this is preferable to mastectomy needs to be assessed by the patient and her physician.

A high risk of systemic relapse is not a contraindication for breast conservation, but a determinant of the need for adjuvant therapy.

Family History

A family history of breast cancer is not a contraindication to breast conservation. Several studies have shown that the rate of breast recurrence in patients with first-degree or second-degree relatives with breast cancer is not different than that seen in patients without a family

history of breast cancer. In breast cancer patients with an inherited germ-line mutation in BRCA 1 or 2, the risk of ipsilateral breast tumor recurrence following BCS and RT is not increased (at least over 10 to 15 years); however, these patients appear to be at a substantially increased risk of contralateral breast cancer, and this should be considered during the treatment counseling process [75-79].

Preoperative Chemotherapy

Patients who are not candidates for breast conservation on the basis of a large tumor in a small breast should be considered for preoperative chemotherapy to reduce the tumor size. This approach is not appropriate for patients with evidence of multicentricity on the initial mammogram or those who prefer treatment by mastectomy. The NSABP has reported the results of two large randomized trials addressing the use of preoperative chemotherapy to increase rates for BCT. In the B18 trial 1,523 patients with TI-3 N0-1 breast cancer were randomized to surgery followed by 4 cycles of adriamycin cytoxan (AC) or AC before surgery [80-81]. At 5 years of follow-up, no differences in disease-free or overall survival were seen. Breast conservation could be performed in 67.8% of patients having preoperative chemotherapy versus 59.8% having initial surgery (p=0.003). Overall, no difference was seen in the incidence of breast recurrence between the preoperative (7.9%) and the postoperative (5.8%) group. However, among patients able to undergo lumpectomy only after downstaging by chemotherapy, the local failure rate was 14.5%, compared to 6.9% in those believed to be candidates for breast conservation before chemotherapy (p=0.04). In the B27 study, the impact of adding 4 cycles of docetaxol (T) to AC was examined. Although the addition of T significantly increased the rate of both clinical and pathologic complete response compared to treatment with AC alone, no increase in the rate of BCT was observed in patients receiving preoperative T [82]. This undoubtedly reflects the difficulty in assessing the extent of residual viable tumor after preoperative chemotherapy. MRI shows promise in this regard, but difficulties in detecting small amounts of residual tumor remain. Overall, approximately 25% of patients who would require mastectomy if operated on at presentation can undergo BCT after preoperative chemotherapy [83]. Patients most likely to benefit from this approach are those with unicentric, high-grade, estrogen receptor negative cancers. A meta-analysis of 9 randomized trials of preoperative chemotherapy has demonstrated no decrease in survival with this approach. However, an elevated risk of locoregional recurrence (RR1.22, 95% CI 1.04–1.43) was noted [84]. In the NSABP B18 study the increased risk of recurrence was observed regardless of patient age or tumor size, and it emphasizes the need for careful attention to evaluation of the extent of disease and the technical details of resection and RT planning in these patients. Neoadjuvant endocrine therapy has also been used successfully to increase rates of breast conservation in patients with hormone receptor positive tumors, although there is less experience with this approach than with chemotherapy.

Percutaneous placement of tumor marker clips within the primary tumor is recommended to provide a landmark for localization and excision should a clinical and radiographic complete response to chemotherapy occur [85].

The accuracy of sentinel node biopsy after chemotherapy has also been a source of controversy. Many of the initial studies of this approach had small sample sizes and very heterogeneous patient populations, making the results difficult to evaluate. Mamounas et al reported the results of sentinel node biopsy in a subset of 428 patients in the NSABP B27 trial who had a sentinel node biopsy followed by an axillary dissection [86]. A sentinel node was identified in 85% of patients, and the false negative rate was 11.9%. The accuracy of the sentinel node procedure did not vary based on the degree of pathologic response in the breast. These results are comparable to those reported for primary sentinel node biopsy during the same time period. Although sentinel node biopsy was not part of the protocol design of the B27 study, these data provide reassurance that in the patient who is clinically node negative at presentation; sentinel node biopsy after chemotherapy is an accurate method for staging the axilla. In the subset of patients where knowledge of the histologic nodal status at presentation is important for radiation treatment planning, sentinel node biopsy should be performed prior to the administration of chemotherapy. An initial multidisciplinary evaluation of patients being considered for preoperative chemotherapy is particularly useful in making decisions about the timing of sentinel node biopsy. Insufficient data exist on the accuracy of sentinel node biopsy in patients who are node positive at presentation and whose palpable nodes resolve with chemotherapy to recommend this approach outside of a trial setting.

IV. TECHNICAL ASPECTS OF SURGICAL TREATMENT

When breast conservation treatment is appropriate, the goals of any surgical procedure on the breast are total gross removal of the suspicious or known malignant tissue with minimal cosmetic deformity. These goals apply to either a diagnostic biopsy or a definitive local excision prior to radiation therapy. Failure to consider them at all stages may jeopardize conservation of the breast. Needle biopsy is the preferred method of diagnosis of both palpable and nonpalpable breast lesions.

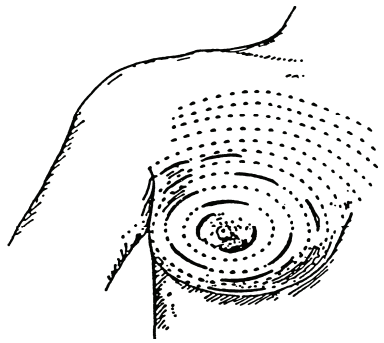

Figure 1. Recommended locations of incisions for performing lumpectomy. For larger lesions in the lower breast, particularly when skin must be excised, a radial incision often results in better cosmesis. *(Reprinted with permission from Bland KI, Copeland EM,eds. The Breast: Comprehensive Management of Benign and Malignant Disease. Philadelphia, PA: WB Saunders; 1998:802–816.)*

A. Skin Incision

The placement and performance of the skin incision can be critical to the quality of cosmesis. Curvilinear skin incisions following Langer's lines generally achieve the best cosmetic result (Figure 1). However, at the 3 o'clock and 9 o'clock positions and in the lower breast, a radial incision may provide a better result**,** particularly if skin removal is necessary.

The incision should be over or close to the tumor and of adequate size to allow the tumor to be removed in one piece. In the upper inner aspect of the breast, some retraction of the skin may be necessary to avoid an incision that may be visible with clothing. Periareolar incisions for lesions in the periphery of the breast are inappropriate.

Excision of a segment of skin is rarely necessary and is undesirable because it may alter the position of the nipple or the inframammary crease. Preservation of the subcutaneous tissue with separate closure improves the cosmetic result. The skin should be closed with a subcuticular technique.

B. Breast Tissue Management

The primary lesion should be excised with a rim of grossly normal tissue, avoiding excessive sacrifice of breast tissue. Very superficial tumors in the subareolar area may require excision of the nipple areolar complex to assure adequate tumor margins and to avoid devascularization. (Partial areolar excision with careful approximation for small lesions in the immediate subareolar area can provide adequate tissue removal and good cosmesis.) Closure of the breast tissue may reduce the occurrence of a saucer-like defect, but the overall cosmetic result with nipple areolar sacrifice will be less than optimal.

Lesions within the substance of the breast should be approached by incising the overlying breast tissue. A superior cosmetic effect is usually achieved when the breast is not reapproximated. Reapproximation that appears to be adequate with the patient relaxed and supine often results in distortion of the breast when the patient is upright and mobile.

Meticulous hemostasis is of critical importance. Hematoma formation produces changes that are difficult to interpret by physical examination. In addition, the evolving scar from a hematoma makes mammography interpretation difficult. These changes may be long-lasting and lead to unnecessary biopsy because of the difficulty in evaluation.

Drains in the breast should be avoided.

Specimen orientation by the surgeon with the use of sutures, clips, multicolored indelible ink, or another suitable technique is important. The specimen should not be sectioned before it is submitted to the pathologist. The surgeon should examine the specimen for the determination of a grossly clear margin. If a clear margin is not evident, re-excision should be performed at that time. Routine frozen section evaluation of margins is optional and does not guarantee negative margins after a complete examination. Any uncertainty regarding orientation of the specimen should be clarified for the pathologist by the surgeon. In addition, clips outlining the breast defect may aid the planning and execution of radiation therapy and demarcate the tumor bed for future imaging studies.

C. Image-Directed Surgery

Nonpalpable carcinoma may be diagnosed by image-directed biopsy or needle localization and excision. Image-directed biopsy is more cost effective and allows a discussion of treatment options prior to the placement of an incision on the breast. It also allows surgery on the primary tumor and the axilla in a single operation, making it the preferred diagnostic technique unless specific contraindications are present. If a patient has a nonpalpable carcinoma diagnosed by image-guided biopsy, then breast-conserving surgery should be conducted with presurgical localization with a guide such as guidewire. This will be facilitated by the placement of a marker clip when image-guided biopsy is done for small lesions, which are likely to be completely removed by the procedure.

Suspicious lesions detected by mammography require presurgical localization in order to assure accurate

removal of the abnormal area and avoid excess sacrifice of breast tissue. The methods of localization may be by needle-hookwire, blue dye injection, or a combination of both. The localization should be precise. Labeled craniocaudal and lateral films that show the hookwire should be sent to the operating room for the surgeon's orientation. The surgeon usually should assess the exact location by triangulation based on the position, depth of penetration, and angle of the wire and place the incision closest to the tip of the wire in order to achieve the best cosmetic result. Tunneling should be avoided, and attempts should be made to make the skin incision as close to the lesion as possible (Figure 2). The same principles of skin incision and breast tissue management used for palpable cancers should be employed.

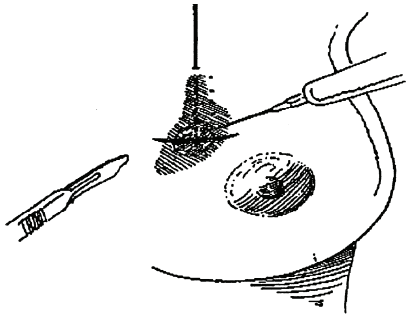

Figure 2A. Incision placement for needle localization biopsy should be over the lesion, not at the point of entry of the wire into the breast.

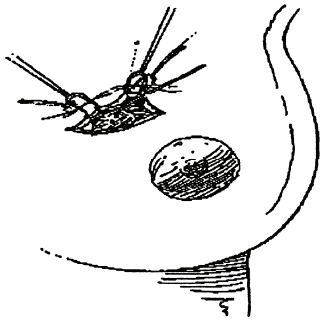

Figure 2B. The breast tissue is dissected until the wire is identified within the parenchyma, and then the wire is stabilized distally and brought into the field. Traction on the wire should be avoided at all times. (*Figures reprinted with permission from Silen W, Matory EJ, Jr., Love S. Atlas of Techniques in Breast Surgery. Philadelphia, PA: Lippincott-Raven; 1996;53–54).*

Localization titanium clips may be left in the excision cavity to aid in placement of the irradiation boost volume and to ensure adequate coverage with tangential fields, especially for lateral and medial lesions.

D. Specimen Radiograph

A radiograph of the specimen should be obtained to document that the occult lesion or needle biopsy clip has been removed. A second radiograph after the specimen has been inked and sectioned by the pathologist provides additional information regarding the radiographic margins of the lesion or microcalcifications.. Magnification and compression of the specimen will increase the resolution of the radiograph but may artificially decrease the anterior and posterior margin measurements. The specimen film should be correlated with a preoperative mammogram and interpreted without delay. The radiologist's report should indicate whether the mammographic abnormality (mass or calcifications) is seen in the specimen and if it has been removed completely, as far as can be determined. The proximity of the abnormality to the edge of the resected tissue should be noted. The radiologist should communicate these findings to the surgeon in the operating room so that additional tissue can be removed if necessary. Subsequent specimens also should be radiographed. Specimen radiography may be useful in confirming removal of masses that are palpable intraoperatively to ensure that they correspond to the mass lesion seen mammographically.

E. Re-excision of Biopsy Site

Re-excision of the previous biopsy site to assure negative margins of resection must be carefully performed in order to accomplish this goal, avoid excess breast tissue removal, and achieve good cosmesis. Proper orientation of the original biopsy specimen (for example, short suture in the superior margin, long suture in the lateral margin) will allow identification of the individual margin surfaces involved with tumor. Re-excision can be limited to those areas. When the specimen has not been oriented, removal of a rim of tissue around the entire previous biopsy is necessary.

For larger biopsy cavities, shaving of each individual margin, with marking of the new margin surface with sutures, clips, or ink, allows removal of residual tumor with preservation of a maximum amount of breast tissue. For very small cavities, removal of the entire biopsy site as an en bloc specimen is acceptable.

F. Special Considerations in Patients Receiving Preoperative Chemotherapy

Additional breast imaging studies should be obtained following the planned course of chemotherapy to assess the patient's suitability for breast-conserving therapy. However, mammography does not reliably exclude persistent microscopic tumor, and architectural distortions and calcification do not always indicate residual disease. Breast MRI may be a more accurate method of assessing

the extent of residual invasive tumor when expertise with this technique is available [37,38].

The initial surgical resection in these patients should include the removal of any clinically or radiographically abnormal tissue. If viable tumor is present throughout the specimen, even if it does not extend to the margin, a further re-excision should be considered. If additional viable tumor is present in the re-excised specimen, a re-evaluation of the patient's suitability for breast conservation is necessary.

G. Management of the Axillary Nodes

1. Level I and II axillary lymph node dissection is indicated in patients who present with unequivocally positive nodes or nodes that have been documented to contain metastases by needle biopsy or FNA.

   Axillary dissection is the standard technique for managing axillary nodes involved with tumor. A level I and II axillary dissection will provide accurate staging information and maintain local control in the axilla. In the patient undergoing mastectomy, axillary dissection should be performed through the mastectomy ellipse. In the patient undergoing breast conservation, the breast incision and the axillary incision should be separate. A continuous incision from the breast to the axilla results in unnecessary deformity. Occasionally, a tumor in the axillary tail can be removed through the same incision used to remove the axillary nodes. A transverse incision in the low axilla from just posterior to the border of the pectoralis major to nearly the anterior border of the latissimus dorsi obtains an excellent cosmetic result and excellent exposure. Some surgeons prefer a vertical incision posterior and parallel to the border of the pectoralis major, which also provides good exposure and cosmetically good results. During dissection, the long thoracic nerve, the thoraco dorsal nerve, and the medial pectal nerve should be preserved. Preservation of the intercostal brachiocutaneous nerve is desirable, as numbness of the posterior upper arm is less likely to occur with nerve preservation. At times, preservation of this nerve should not be performed because of grossly involved lymph nodes. Stripping of the axillary vein is unnecessary and should be condemned because it increases the incidence of lymphedema. Usually, closed suction drainage is advisable.

2. Sentinel lymphadenectomy

   Proof of the concept that a sentinel node(s) which reliably predicts the status of the remaining axillary nodes can be identified in more than 90% of women with breast cancer was obtained from multiple individual and multi-institutional studies [87-93]. Lymphatic mapping for sentinel lymph node dissection can be accomplished with 1% isosulfan blue dye or radiolabled colloids. Usually, a combination of technetium sulfur colloid and dye is used [89]. In the nonrandomized studies that provided proof of the sentinel node concept, a major concern was the 5% to 10% false negative rate of sentinel node biopsy when compared to immediate axillary dissection. Two prospective randomized trials have directly compared the identification of nodal metastases with sentinel node biopsy or axillary dissection and found no difference in the rate of identification of metastases [92,93].

   Studies of local recurrence after sentinel node biopsy alone in patients with histologically negative sentinel nodes document extremely low rates of isolated axillary recurrence. One group reported only one axillary recurrence out of 592 sentinel node-negative patients followed with observation alone (0.17%) [94]. Smidt et al [97] identified two axillary recurrences in 439 patients (0.46%) after a median follow-up of 26 months. They also reported a literature review of 3,184 sentinel lymph node biopsy-negative patients with a median follow-up of 25 months. Axillary recurrence occurred in eight patients after a median of 21 months, an axillary recurrence rate of 0.25%. Of the patients with axillary recurrence, nearly one-third presented with synchronous systemic metastases.

   Additional data on the accuracy of sentinel node biopsy and the incidence of isolated axillary recurrence will be available from three major clinical trials studying the procedure under the auspices of the NSABP, the ACOSOG, and the Royal Australian College of Surgeons.

   The utilization of new procedures demands proper training and validation. Surgeons should not undertake the procedure independently. They need to work closely with nuclear medicine, diagnostic radiology, and operating room personnel, and with pathology.

   Surgeons should perform both sentinel node biopsy and axillary lymph node dissection until they are confident that the procedure can be

performed with identification of sentinel nodes in at least 90% of patients with a false-negative rate of 10% or less. For most surgeons, this requires 20 to 30 sentinel node biopsies followed by axillary dissection.

Current contraindications to sentinel node biopsy include pregnancy and lactation, locally advanced breast cancer, and prior axillary surgery. If sentinel node biopsy is performed in the presence of clinically suspicious adenopathy, care must be taken to remove the suspicious nodes even if they do not take up blue dye or radioactivity since lymphatic channels that are blocked with tumor may prevent uptake of these agents. An alternate approach in the patient with truly suspicious adenopathy is to establish a preoperative diagnosis with a needle biopsy.

Sentinel node biopsy allows the pathologist to perform a more detailed examination of the sentinel node than was possible when evaluating an entire axillary dissection specimen. This has resulted in the increasingly frequent detection of very small metastases. In general, patients with metastases in sentinel nodes detected by hematoxylin and eosin should undergo complete Level I and II axillary dissection. Immunohistochemistry should not be routinely performed, as the significance of metastases in sentinel nodes detected only by immuno-histochemistry remains to be determined. Therapeutic decisions should be made on the basis of metastases identified by hematoxylin and eosin staining.

Sentinel node biopsy usually results in minimal morbidity. One series reported a decrease in arm lymphedema from axillary lymph node dissection from 17.1% to 2% for sentinel node dissection [94]. In the randomized trial performed by Veronesi et al significant differences in pain, paresthesia, and lymphedema between axillary dissection and sentinel node biopsy were present at both 6 and 24 months postoperatively [94].

Rehabilitation after axillary lymph node dissection or sentinel node biopsy is essential. Usually, patients after sentinel node biopsy require no formal exercise to return to full function. Patients after axillary dissection should be given formal exercise training to prevent a frozen shoulder. Use of shoulder immobilization and arm slings or wraps should be avoided, as these contribute to a frozen shoulder. If a patient does not achieve early recovery or full shoulder function (by 6 to 8 weeks), physical therapy should be instituted to avoid permanent dysfunction.

Although many believe that sentinel lymph node biopsy for clinically node negative breast cancer has become the standard of care, longer follow-up and clinical trial results will form a firmer foundation for the procedure.

V. TECHNIQUES OF IRRADIATION

A multidisciplinary approach is necessary for optimal breast conservation treatment. Radiation therapy should be delivered only after evaluation of the mammography findings, the pathology findings, and the surgical procedures performed on the patient. The optimal combination of surgery and irradiation to achieve the dual objectives of local tumor control and preservation of cosmetic appearance varies from patient to patient. The optimal combination is determined by the extent, nature, and location of the tumor, the patient's breast size, and the patient's relative concerns about local recurrence and preservation of cosmetic appearance. Close cooperation between radiation oncologists and medical oncologists also is important because irradiation and adjuvant chemotherapy require integration if both treatment modalities are used.

A. Elements in the Technique of Irradiation

There is a general consensus regarding some but not all of the elements in the technique of irradiation. Treatment facilities should conform to American College of Radiology practice guidelines and technical standards for radiation oncology facilities. As soon as the patient has healed adequately from the surgical procedure, radiation therapy should begin. Therefore, irradiation usually can begin within 2 to 4 weeks of uncomplicated breast-conserving surgery.

The radiation oncologist should use measures to assure reproducibility of patient set-up, treatment simulation, treatment planning, and choice of supervoltage equipment to assure dose homogeneity. High-energy photons (≥10 MV) may be indicated for very large-breasted women or patients with significant dose inhomogeneity on treatment planning using lower energy photons.

The radiation oncologist can use sophisticated treatment planning that involves three-dimensional rather than two-dimensional dose distributions and accounts for the lower density of lung tissue in the treatment field. (In standard treatment planning, the lung is considered to have unit density.) However, the impact of this recent development on patient outcomes has not been demonstrated.

Each field should be treated on a daily basis, Monday through Friday. Bolus should not be used. To minimize

the risk of radiation pneumonitis, not more than 3 to 3.5 cm of lung as projected on the beam radiograph at isocenter should ordinarily be treated, and a minimum of 1 to 1.5 cm of lung is required. For left-sided lesions, efforts should be made to minimize the amount of heart in tangential fields. Whole-breast radiation therapy is delivered using opposed tangential fields to a dose of 4,500 to 5,000 cGy at 180 to 200 cGy per fraction.

Although controversy has existed concerning the need for delivering an additional boost dose to the primary site, there is growing consensus about its utility. Most recently the EORTC has reported the favorable impact of boost on local failure rates. Several considerations may be involved in the decision to use a boost: histological studies show that residual cancer following resection of the primary usually is in the vicinity of the primary site; recurrences following treatment usually are seen at or near the primary site; and boost treatment can be delivered without significant morbidity. Although boost irradiation generally is used, the precise indications for its use are not well defined. However, research indicates that a boost should be used in patients with focally positive or close margins of resection.

Boost irradiation usually is delivered using electron beam or interstitial implantation. The total dose to the primary tumor site is increased to approximately 6,000 to 6,600 cGy. Selection of the boost dose and volume should be based on knowledge of the surgical procedure and the pathologic findings. In situations where an electron beam boost and an interstitial implant boost are judged to be equally effective, an electron beam is generally preferred because of considerations of cost, patient convenience, and cosmesis.

A boost may not be required for patients who have been treated with more extensive breast resections and have margins of resection that are clearly negative. If the breast boost is omitted in these patients, the only available data indicate that the standard whole- breast radiation therapy dose is 5,000 cGy at 200 cGy per fraction.

B. Techniques To Be Avoided

Although there is a lack of consensus concerning the advisability of treating nodal areas with irradiation, there is agreement on the need to avoid certain radiation therapy techniques for treating regional lymph nodes:

1. Axillary irradiation usually is unnecessary following a complete axillary dissection (Levels I to III). Irradiation of the supraclavicular fossa and contiguous apical region may be considered if extensive numbers of lymph nodes (e.g., ≥4) contain tumor. The benefit of radiation in patients with one to three positive nodes is unknown.
2. Overlap between adjacent fields should be avoided.
3. Techniques that result in cardiac irradiation should be avoided given the known increase in late cardiac mortality with inadvertent irradiation of the heart. The use of computed tomography (CT) simulation is encouraged for patients with left-sided breast cancer to aid in minimizing cardiac irradiation.

VI. FOLLOW-UP CARE

Follow-up assessment of the results of breast conservation treatment emphasizes the cosmetic outcome as well as the functional consequences. Regular follow-up examination includes the following goals:

1. Early detection of recurrent or new cancer, allowing timely intervention.
2. Identification of any treatment sequelae and appropriate interventions where indicated.
3. Providing the individual practice with the database necessary to optimize treatment and compare outcomes against national standards.

Regular history and physical examination in conjunction with breast imaging are the cornerstones of effective follow-up care. Unfortunately, many patients perceive history and physical examination to be less important as reliable follow-up measures than sophisticated medical testing. A public education effort is needed to address this problem.

The physician should perform the following evaluations at cited intervals following the completion of treatment:

A. Examinations and Mammography

1. History and physical examination

   Local failure occurs at constant rate from years 2 through 8 post-treatment; therefore, examination frequency should be based on risk factors for both local and distant recurrence.

   a. Examination frequency

   Many patients are treated by a team of physicians. It is not necessary for each physician to see the patient at 3 to 6 month intervals provided that good communication between providers is maintained.

   - Every 3 to 6 months, years 1 through 3. This will vary for patients receiving adjuvant

chemotherapy who need more frequent assessment during the course of their active treatment.

- Every 6 months, years 4 and 5. Some investigators prefer to continue semiannual examinations through year 8 because the rate of local recurrence is constant through that time interval.
- Annually after year 5. More frequent follow-up for patients at exceptionally high risk may be needed.

2. Mammography

A goal of follow-up imaging of the treated breast is the early recognition of tumor recurrence. To prevent unnecessary biopsy, it is important to know that postoperative and irradiation changes overlap with signs of malignancy on a mammogram. The changes include masses (postoperative fluid collections and scarring), edema, skin thickening, and calcifications [98-103].

At times, these changes may be impossible to distinguish. Postsurgical and radiation edema, skin thickening, and postoperative fluid collections will be most marked in the first 6 months. After the first 6 to 12 months, radiographic changes will slowly diminish, and demonstrate stability within 2 years for most patients.

In order to interpret mammograms accurately and assess the direction of change, the current mammogram must be compared in sequence to preceding studies. The diagnostic radiologist can tailor mammographic studies of the treated breast to the surgical site by using special mammographic views in addition to routine mediolateral oblique and craniocaudal views. Magnification and spot compression can be used with any view to increase detailed visualization of the site of tumor excision and other areas. Magnification mammography is useful to classify calcifications morphologically and quantitate them. In some cases, a view with the X-ray beam tangential to the scar and various other additional obliquities will be helpful to differentiate recurrent tumor from postprocedural changes.

Ultrasonography can characterize a postoperative mass, such as a seroma, as fluid-filled rather than solid. As these masses resolve and scars form, a spiculated soft tissue density that mimics tumor may be seen on the mammogram. Additional radiographic projections of the site of tumor removal may facilitate more confident radiographic interpretations.

a. Schedule of imaging of the treated breast

Postoperative, preradiation therapy mammography is particularly important after malignant microcalcifications have been removed or if the adequacy of the resection is questioned. Magnification mammography can be useful in identifying or verifying possible residual malignant calcifications.

A baseline mammogram for comparison should be performed 6 to 12 months after tumor excision and completion of radiation, and at least annually thereafter, or at more frequent intervals as warranted by clinical or radiographic findings.

b. Schedule of imaging of the contralateral breast

Mammography should be performed annually, according to the guidelines endorsed by both the American College of Radiology and the American Cancer Society and with synchronization of surveillance mammography of the treated breast. More frequent intervals may be warranted by clinical or radiographic findings. (The risk of cancer is approximately the same for both the treated and untreated breast.)

B. Other Tests

Symptomatic patients are justifiably evaluated with other medical tests (e.g., radionuclide bone scan, chest radiography**,** CT scans, liver function tests) as indicated by the character of their medical problem. An annual chest X-ray in patients who smoke may be appropriate. Randomized controlled trials have shown that routine use of these tests has provided no benefit for asymptomatic patients with Stage I or II breast carcinoma. No survival benefits have been demonstrated, and the cost-effectiveness of using such procedures in routine follow-up is seriously in question.

(See the American College of Radiology, Imaging Workup for Stage I Breast Carcinoma, ACR Appropriateness Criteria®, 2002. Available at http://www.acr.org.)

C. Evaluation of Sequelae

At the time of the first follow-up examination and serially thereafter, the physician should evaluate the patient for any treatment-related toxicities. This evaluation should include:

1. Assessment of the overall cosmetic result. A four-point scoring system is recommended for assessing the cosmetic result (Appendix A).
2. Assessment of complications. Complications should be specified with regard to symptomatology and physical findings. The use of the RTOG/EORTC Radiation Toxicity Scoring Scheme is recommended for the grading of complications. In addition, the simple measurement of arm circumference at fixed distances above and below the olecranon is recommended for the evaluation and quantification of arm edema.
3. Patient evaluation of results. The patient's evaluation of treatment outcomes in terms of psychological, functional, and cosmetic consequences should be taken into account in the follow-up process.

APPENDIX A

FOUR-POINT SCORING SYSTEM OF BREAST COSMESIS

Excellent
Treated breast almost identical to untreated breast.

Good
Minimal difference between the treated and untreated breasts.

Fair
Obvious difference between the treated and untreated breasts.

Poor
Major functional and esthetic sequelae in the treated breast.

Table 1: Prospective Randomized Trials Comparing Conservative Surgery and Radiation with Mastectomy for Early-Stage Breast Cancer

Trial	Treatment Period	Number of Patients	Stage	Surgery for Primary	Adjuvant Therapy
Milan I [1-2]	1973 to 80	701	I	Q, RM	CMF
Institut Gustav Roussy [3]	1972 to 80	179	I	WE MRM	None
NSABP B06 [4-5]	1976 to 84	1219	I to II	WE MRM	Melphalan F
National Cancer Institut [6]	1979 to 87	237	I to II	WE MRM	AC
EORTC [7-8]	1980 to 86	868	I to II	LE MRM	CMF
Danish Breast Cancer Group [9]	1983 to 89	904	I to III	Q,WE MRM	CMF T

Q=quandrantectomy WE=wide excision LE=local excision RM=radical mastectomy MRM=modified radical mastectomy C=cyclophosphamide M=methotrexate F=5-fluorouracilA=doxorubicin T=tamoxifen EORTC (European Organization for Research and Treatment of Cancer)

NEW Table 2: Survival Comparisons for Conservative Surgery and Radiation (BCS&XRT) Versus Mastectomy in Prospective Randomized Trials

Trial	Endpoint	Overall Survival % BCS& RT/		Mastectomy	Disease-Free Survival % BCS& RT/		Mastectomy
Milan I [2]	20 years	42	(NS)	41			
Institut Gustave-Roussy [3]	15 year	73	(.19)	65			
NSABP B06 [4]	20 years	46	(.74)	47	35	(.41)	36
National Cancer Institute [6]	20 years	54	(.67)	58	63	(.64)	67
EORTC [7]	10 years	65	(NS)	66			
Danish Breast Cancer Group [9]	6 years	79	(NS)	82	70	(NS)	66

( )=p value NS=not significant

New Table 3: Comparisons of Local Recurrence Following Conservative Surgery and Radiation (BCS + RT) or Mastectomy in Prospective Randomized Trials

Trial	Endpoint	BCS +	RT	Mastectomy
Milan I [2]	Cumulative incidence at 20 years	9%	(NS)	2%
Institut Gustave Roussy [3]	Cumulative incidence at 15 years	9%	(NS)	14%
NSABP B06 [4]	Crude incidence at 20 years	14%		10%
National Cancer Institut [6]	Crude incidence +/- regional/distant 20 years	31%		6%
EORTC [7,8]	Actuarial at 10 years	20%	(.01)	12%
Danish Breast Cancer Group [9]	Crude incidence median follow-up 3.3 years	3%	(NS)	4%

( )=p value NS=not significant

New Table 4: Prospective Randomized Trials Comparing BCS With and Without RT

Trial	Number of Patients	Tumor Size (cm)	Pathologic Nodal Status	Surgery	Systemic Therapy
NSABP B-06 [4]	1,265	≤ 4	N+ or N-	L	L-Pam 5FU for N+
Milan III [16,17]	601	≤ 2.5	N- or N+	Q	CMF or Tamoxifen N+
Uppsala-Orebro [18]	381	≤ 2	N-	Q	None
Ontario [19]	837	≤ 4	N-	L	None
NSABP B-21 [20]	1,009	≤ 1	N-	L	Tamoxifen
Scottish [21]	556	≤4	N- or N+	WE	CMF or Tamoxifen N+
St. George's, UK [22]	399	≤ 5	N- or N+	WE	CMF or Tamoxifen
BASO II, UK [23]	241	≤ 2	N-	WE	Tamoxifen
West Midlands [24]	707	≤ 4	Clin N-	WE	Tamoxifen
Swedish [25]	1,187	≤ 5	N-	Q	Tamoxifen in a few
CALGB [26]	636	2	N-	L	Tamoxifen
Canadian [27]	769	≤ 5	N-	L	Tamoxifen
CRC, UK [28]	518	?	?	WE	Chemo or Tamoxifen
Finnish [29]	152	≤ 2	N-	WE	None

5FU = 5-fluorouracil CMF = Cyclophosphamide, Methotrexate, 5-fluorouracil
L = local excision WE = wide excision Q = quadrantectomy

Table 5: Local Recurrence and Survival in Prospective Randomized Trials Comparing BCS With and Without RT

Trial	Breast Recurrence % BCS	Breast Recurrence % BCS+RT	Overall Survival % BCS	Overall Survival % BCS+RT	Interval Results Reported
NSABP B-06 [4]	39	14	46	46	20-year actuarial
Node Negative	36	17			No systemic Rx
Node Positive	44	9			Systemic Rx
Milan III [16,17]	18	2	92	92	5-year actuarial
Uppsala-Orebro [18]	24	9	78	78	10-year actuarial
Ontario [19]	40	18	72	74	10-year actuarial
NSABP B-21 [2]	17**	3**			8-year actuarial
Scottish [21]	28	6	93	93	5-year actuarial
ER-positive	25	3			
ER-negative	44	14			
St. George's, UK [22]	35	13			5-year actuarial
BASO II, UK [23]	5	2	98	98	Crude 4-year median
West Midlands [24]	13	4			Crude 2-year mean
Swedish [25]	14	4	93	94	5-year actuarial
CALGB [26]	4*	1*	86	87	5-year actuarial
Canadian [27]	7.7	0.6	93	93	5-year actuarial
	17.6	3.5			8-year actuarial
CRC, UK [28]		69 % reduction		No difference	Crude 9.7 year median
Finnish [29]	18.1	7.5	99^	98^	Crude with mean FU=6.7 years

* local regional recurrence ^ 5-year cancer-specific survival
** both groups given tamoxifen

Table 6: Elements of the Breast Cancer Specific History

- Family history – Relatives with breast cancer (age at diagnosis, laterality), ovarian carcinoma
- History of prior therapeutic irradiation involving breast region
- History of collagen vascular disease – type, documentation of diagnosis
- Presence of breast implants – submammary or subpectoral
- Date of last menstrual period/possibility of pregnancy
- Symptoms suggestive of metastasis

Table 7: Elements of the Breast Physical Exam

- Tumor size (measured) and location
- Fixation to skin
- Ratio of breast size to tumor size
- Evidence of multiple primary tumors
- Axillary node status – size, mobility
- Supraclavicular nodes
- Evidence of locally advanced cancer
  - skin ulceration, satellitosis
  - peau d'orange
  - inflammatory carcinoma
  - fixed axillary nodes
  - lymphedema of the ipsilateral arm

Table 8: Recurrence Rates Following Conservative Surgery and Radiation Therapy by Margin Status

Author (Institution)	Number of Patients (Medium FU)	Endpoint	Negative	Close	Positive
Borger et al [58] Netherlands	1,026 (5.5 yrs)	5-yr actuarial	2%	6%	16%
Dewar et al [42] (Gustave-Roussy)	757 (9 yrs)	10-yr actuarial	6%	14%	
Freedman et al [59] (Fox Chase)	1,262 (6.3 yrs)	10-yr actuarial	7%	14%	12%
Park et al [60] (JCRT)	533 (10.6 yrs)	8-yr crude rate	7%	7% 27%**	14%*
Anscher et al [61] (Duke)	259 (3.7 yrs)	5-yr actuarial	2%	10%	
Smitt et al [62] (Stanford)	535 (6 yrs)	6-yr actuarial	3%	22%	17%
Santiago et al [63] (U. Penn)	937 (10.1 yrs)	10-yr actuarial	10%	14%	25%
Wazer et al [64](Tufts)	498 (6 yrs)	10-yr actuarial	2%	2%	15%
Pittinger et al [65] (U. Rochester)	211 (4.5 yrs)	Crude rate (f/u=54)	3%	3%	
Obedian, Haffty [66] (Yale)	984 (13 yrs)	10-yr actuarial	2%	2%	18%

* = focally positive ** = more than focally positive

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