

Standards for Diagnosis and Management of Invasive Breast Carcinoma

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

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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, to track changes in patterns over time, and to relate patterns to patient outcomes.

As the treatment of patients with cancer progressively has become multidisciplinary, studies of patterns of care have become more complex. The three Colleges, the American Cancer Society, and the Society of Surgical Oncology have attempted to promote better and more consistent care of cancer patients. Representatives of these groups first met in 1992 to begin the long process of describing standard practice in one specific area, breast-conservation treatment.

The meetings and the resulting guidelines were considered only a point of departure from which to involve other disciplines within medicine, to educate patients, and to establish a framework for developing guidelines for the multidisciplinary management of other types of cancer.

Because knowledge has advanced in a variety of fields related to the treatment of early breast cancer, revising these documents is appropriate. The document published in 1992 focused on the treatment of invasive carcinoma of the breast.¹ The increased use of and improvements in mammographic technology have resulted in a marked increase in the diagnosis of ductal carcinoma in situ (DCIS). The body of knowledge about DCIS that has developed required a separate treatment of this subject in a companion document, "Standards for Diagnosis and Management of Ductal Carcinoma in Situ (DCIS) of the Breast" published in this issue of *CA* on pages 108-128.^{1a}

David P. Winchester, MD, of the American College of Surgeons and James D. Cox, MD, of the American College of Radiology served as co-editors for this report, which was approved by the American College of Radiology, the American College of Surgeons, the Society of Surgical Oncology, and the College of American Pathologists.

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Review and Summary of the Literature

Mastectomy (either radical or modified radical) was the historical mainstay of the treatment of stage I and stage II breast cancer for decades. Although mastectomy continues to be appropriate for some patients, breast conservation has become the preferred method of treatment for

many patients. The results of prospective randomized trials and the results of large retrospective nonrandomized studies from single institutions have shown that mastectomy and breast-conservation treatment are equally effective for appropriately selected patients with early-stage breast cancer.

PROSPECTIVE RANDOMIZED TRIALS

Six modern prospective randomized trials have compared mastectomy with conservative surgery and radiation for stage I and II breast cancer (Table 1). Whole breast irradiation with doses of 45 to 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) 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 60 Gy or more.

The published results of these trials are presented in Tables 2 and 3. At a follow-up of up to 18 years, none of the trials show significant differences in overall or disease-free survival with either treatment. In particular, survival has not been found to improve in patients with histologically positive nodes treated with mastectomy and chemotherapy in either the Milan I trial or the NSABP B-06 trial.^{2,3} The Milan I trial showed a survival benefit that was not statistically significant in axillary node-positive patients treated with quadrantectomy and radiotherapy compared with radical mastectomy.³

In five of the six randomized trials, no significant difference was seen in the

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The report is based on several conferences held jointly by the American College of Radiology and the American College of Surgeons during 1996 and 1997, which included the following participants, who are also coauthors: American College of Radiology: James D. Cox, MD (Editor), Professor and Head, Division of Radiation Oncology, M.D. Anderson Cancer Center, Houston, TX; Lawrence W. Bassett, MD, Iris Cantor Breast Professor, UCLA School of Medicine, Los Angeles, CA;

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

Trial	Treatment Period	Total No. of Patients	Stage	Surgery for Primary	Adjuvant Therapy
Milan Cancer Institute Trial I ³	1973–1980	701	I	Quadrantectomy, radical mastectomy	CMF
Institut Gustave-Roussy ²⁵	1972–1980	179	I	Wide excision, modified radical mastectomy	None
NSABP B-06 ^{2,8}	1976–1984	1,219	I-II	Wide excision, modified radical mastectomy	Melphalan, 5-FU
National Cancer Institute ¹⁷	1979–1987	237	I-II	Local excision, modified radical mastectomy	AC
EORTC ^{18,26}	1980–1986	874	I-II	Local excision, modified radical mastectomy	CMF
Danish Breast Cancer Group ²⁷	1983–1989	904	I-III	Quadrantectomy, wide excision, modified radical mastectomy	CMF, T

A = doxorubicin; C = cyclophosphamide; CMF = cyclophosphamide, methotrexate, fluorouracil (5-FU); EORTC = European Organization for Research and Treatment of Cancer; NSABP = National Surgical Adjuvant Breast and Bowel Project; T = tamoxifen.

Table 2
Comparison of Survival after Conservative Surgery and Radiation with That after Mastectomy in Prospective Randomized Trials

Trial	Endpoint (years)	Overall Survival [%]		Disease-Free Survival [%]	
		CS & R (P value)	Mastectomy	CS & R (P value)	Mastectomy
Milan Cancer Institute Trial I ³	18	65 (NS)	65	N/A	N/A
Institut Gustave-Roussy ²⁵	15	73 (.19)	65	N/A	N/A
NSABP B-06 ⁸	12	63 (.12)	59	50 (.21)	49
National Cancer Institute ¹⁷	10	77 (.89)	75	72 (.93)	69
EORTC ²⁶	8	54 (NS)	61	N/A	N/A
Danish Breast Cancer Group ²⁷	6	79 (NS)	82	70 (NS)	66

CS & R = conservative therapy and radiation; EORTC = European Organization for Research and Treatment of Cancer; N/A = data not available; NS = not significant; NSABP = National Surgical Adjuvant Breast and Bowel Project.

risk of a recurrence in the treated breast or chest wall after mastectomy. In the National Cancer Institute (NCI) trial, a significantly higher local failure rate was

observed in the breast-conservation group. However, in this trial, only gross tumor removal was required for study entry. Local recurrence after breast preser-

Table 3
Comparison of Local Recurrence after Conservative Surgery and Radiation with That after Mastectomy in Prospective Randomized Trials

Trial	Endpoint	Local Recurrence (%)		
		CS & R	(P value)	Mastectomy
Milan Cancer Institute Trial ¹³	Cumulative incidence at 18 years	7	(NS)	4
Institut Gustave-Roussy ²⁵	Cumulative incidence at 15 years	9	(NS)	14
NSABP B-06 ²	Cumulative incidence at 8 years	10	(NS)	8
National Cancer Institute ¹⁷	Crude incidence, median follow-up 10.1 years	19	(.01)	6
EORTC ²⁶	Crude incidence at 14 years	17	(NS)	14
Danish Breast Cancer Group ²⁷	Crude incidence, median follow-up 3.3 years	3	(NS)	4

CS & R = conservative surgery and radiation; EORTC = European Organization for Research and Treatment of Cancer; NS = not significant; NSABP = National Surgical Adjuvant Breast and Bowel Project.

vation may be the result of 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 trial.

Overall, the incidence of recurrence in the treated breast ranges from 3% to 19% (Table 3). Most failures in the treated breast can be salvaged with mastectomy, and survival after such treatment is approximately 70% at 5 years.^{4,4a,5} As shown 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 after mastectomy ranges from 4% to 14%. The desire to avoid local recurrence is not a reason to encourage a patient who otherwise is a good candidate for breast conservation to choose mastectomy, because the procedures are associated with an equal risk of local failure.

Nine prospective randomized trials comparing conservative surgery and ra-

diation with mastectomy recently underwent meta-analysis.⁶ No survival differences were found in seven of these trials. Local recurrence was reported in 6.2% of the mastectomized patients and 5.9% of the patients treated with breast conservation.⁶

The randomized trials also have addressed the issue of a second malignancy related to radiation. No difference was seen in the incidence of contralateral breast cancer or that of a second malignancy that was not breast cancer.

In addition to the randomized trials comparing breast conservation consisting of excision and radiation with mastectomy, six randomized trials have compared conservative surgery alone with conservative surgery and radiation. These trials are summarized in Tables 4 and 5. They vary regarding patient selection, the extent of surgery and radiotherapy, and the use of adjuvant systemic therapy. Quadrantectomy was used in the Milan and Swedish studies, and combination chemotherapy

Table 4
Prospective Randomized Trials Comparing Conservative Surgery Alone with Conservative Surgery and Radiation Therapy

Trial	No. of Patients	Tumor Size (cm)	Nodal Status	Surgery	Systemic Therapy
Uppsala-Orebro Breast Cancer Study Group ²⁸	381	< 2.0	Negative	Quadrantectomy	None
Milan Cancer Institute Trial III ^{3, 29}	601	< 2.5	Negative or positive	Quadrantectomy	CMF or tamoxifen for positive nodes
NSABP B-06 ⁸	1,265	< 4.0	Negative or positive	Local excision	L-PAM; 5-FU for positive nodes
Ontario Clinical Oncology Group ³⁰	837	< 4.0	Negative	Local excision	None
Scottish Cancer Trials Breast Group ^{31, 32}	556	< 4.0	Negative or positive	Wide excision	CMF or tamoxifen for positive nodes
British Trial ³³	399	≤ 5.0	Negative or positive	Wide excision	CMF or tamoxifen for positive nodes

CMF = cyclophosphamide, methotrexate, fluorouracil (5-FU); L-PAM = L-phenylalanine mustard; NSABP = National Surgical Adjuvant Breast and Bowel Project.

Table 5
Local Recurrence and Survival in Prospective Randomized Trials Comparing Conservative Surgery Alone with Conservative Surgery and Radiation Therapy

Trial	Breast Recurrence [%]		Overall Survival [%]		Interval Results Reported (years)
	CS	CS + RT	CS	CS + RT	
Uppsala-Orebro Breast Cancer Study Group ²⁸	18	2	90	91	5*
Milan Cancer Institute Trial III ^{3, 29}	18	2	92	92	5*
NSABP B-06 ⁸	35	10	58	62	12*
Ontario Clinical Oncology Group ³⁰	40	18	72	74	10*
Scottish Cancer Trials Breast Group ^{31, 32}	28	6	85	88	5*
ER-positive	25	3	N/A	N/A	N/A
ER-negative	44	14	N/A	N/A	N/A
British Trial ³³	35	13	N/A	N/A	5

CS = conservative surgery; CS + RT = conservative surgery and radiation therapy; ER = estrogen receptor; N/A = data not available; NSABP = National Surgical Adjuvant Breast and Bowel Project.
 *Calculated as actuarial years.

Table 6
Survival after Conservative Surgery and Radiation Therapy
for Early-Stage Breast Cancer in Nonrandomized Studies

Study	No. of Patients	10-Year Survival (%)
Stages I and II		
Fowble et al ³⁴	697	83
Haffty et al ³⁵	278	67
Leung et al ³⁶	493	68
Mansfield et al ⁹	1,070	80*
Spitalier et al ³⁷	1,133	80
Stotter et al ³⁸	490	74
Stage I		
Dewar et al ^{7†}	757	79
Veronesi et al ³⁹	1,232	78
Perez et al ¹⁰	520	85*
Zafrani et al. ^{19b†}	434	86

*Cause-specific.
†Includes small T2.

or tamoxifen was used in the NSABP, Milan, British, and Scottish trials.

Despite these differences, all trials showed a reduction in the rate of recurrence in the breast in the irradiated group (an average crude rate of reduction of 84%, with a range of 73% to 97%). Most women who developed a recurrence in the breast after conservative surgery alone either required or desired mastectomy. Subset analyses within these trials have failed to identify consistently a group of patients who do not benefit from radiation.

NONRANDOMIZED STUDIES

The results of multiple nonrandomized retrospective studies further support the equal effectiveness of breast-conservation treatment and mastectomy in appropriately selected patients (Tables 6 and 7).

At 10 years, overall survival has ranged from 67% to 86%, depending upon the stage of the disease (Table 6). Disease-free survival at 10 years is approximately 70%.^{5,7} These series have also shown excellent long-term control within the treated breast with primary tumors 5 cm in diameter or smaller (Table 7). At 10 years, local recurrence rates range from 8% to 19%. For patients with negative margins of resection, the 10-year actuarial risk of breast recurrence is 10% or less.⁸⁻¹¹

The overall survival and local control rates in the breast reported by these retrospective series are comparable to the results of the six prospective randomized trials.

Patient Selection and Evaluation

Because of the potential options for treatment of early-stage breast cancer, careful

Table 7
Recurrence in the Breast after Conservative Surgery and Radiation Therapy for Early-Stage Breast Cancer in Nonrandomized Studies

Study	No. of Patients	Maximum Primary Tumor Size (cm)	Breast Recurrence at 10 Years (%)
Clark et al ⁴⁰	1,130	5	14
Dewar et al ⁷	757	3	8
Fourquet et al ¹²	518	5	11
Fowble et al ³⁴	697	5	18
Gage et al ⁴¹	1,628	5	13
Haffty et al ³⁵	433	5	19
Halverson et al ⁴²	511	5	14
Kurtz et al ^{4a, 43}	1,593	5	14
Leung et al ³⁶	493	5	10
Mansfield et al ⁹	1,070	5	14
Stotter et al ³⁸	490	5	19
Veronesi et al ⁴⁴	1,232	2	8

patient selection and a multidisciplinary approach are necessary. Four critical elements in patient selection for breast-conservation treatment are history and physical examination, mammographic evaluation, histologic assessment of the resected breast specimen, and assessment of the patient's needs and expectations.

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. 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 examination are listed in Tables 8 and 9. Retractions of skin, nipple, and breast parenchyma are not signs of lo-

cally advanced breast cancer and are not contraindications to breast conservation.

MAMMOGRAPHIC EVALUATION

Recent preoperative mammographic evaluation is necessary to determine a patient's eligibility for breast conservation treatment. It should be done with high-quality, dedicated mammographic equipment in a facility certified by the US Food and Drug Administration under the Mammography Quality Standards Act.

Recent (usually within 3 months) mammographic evaluation, before biopsy or definitive surgery, plays an important role in establishing the appropriateness of breast-conservation treatment. Mammographic evaluation defines the extent of a patient's disease, the presence or absence of multicentricity, and other factors that might influence the treatment decision and evaluates the contralateral breast. Bilateral mammography is needed for palpable lesions and nonpalpable lesions

Table 8
Elements of the History Specific for Breast Cancer

Family history: Relatives with breast cancer, including age at diagnosis; bilaterality; and ovarian carcinoma, endometrial carcinoma, or other malignancies
 Previous therapeutic irradiation involving the breast region
 Previous collagen vascular disease, including type and documentation of diagnosis
 Presence and location (submammary or subpectoral) of breast implants
 Date of last menstrual period/possibility of pregnancy
 Nipple discharge, including whether spontaneous or induced and color
 Symptoms suggestive of metastasis

that can be identified only radiographically. An increasing percentage of carcinomas treated with breast conservation are nonpalpable masses and microcalcifications.

The breast tumor should be measured in at least two dimensions on the mammographic views or from the sonogram during ultrasonography, if it is performed. The size of the tumor should be included in the mammographic report. If the tumor is a poorly marginated 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 the mass should be made. Dimensions of the area in which calcifications are located should be given. 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 are important for characterizing microcalcifications and defining the margins of masses.

Table 9
Elements of Physical Examination of the Breast

Tumor size (measured) and location
 Fixation of tumor to skin
 Ratio of breast size to tumor size
 Evidence of multiple primary tumors
 Axillary node status, including size and mobility
 Supraclavicular node status
 Evidence of locally advanced cancer, including the following:
 Skin ulceration, satellitosis
 Peau d'orange
 Inflammatory carcinoma
 Fixed axillary nodes
 Lymphedema of the ipsilateral arm

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.

PATHOLOGIC FEATURES INFLUENCING TREATMENT CHOICE

Numerous 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 of DCIS in association with an invasive ductal carcinoma, margins of resection, and the status of the axillary nodes.

The presence of vascular or lymphatic invasion, tumor necrosis, and an inflammatory infiltrate have been associated with a somewhat increased risk of breast cancer recurrence. This risk is approximately 10% to 15% at 5 years.^{5,12-14} Some series have also found an increased risk of breast cancer recurrence in patients with high histologic grade tumors compared with those who have low-grade tumors,^{7,13,14} although this has not been a consistent finding.⁵ Histologic subtype other than invasive ductal carcinoma does not appear to be associated with an increased risk of breast cancer recurrence.^{15,16}

Patients with invasive lobular cancers are candidates for conservative surgery and radiation if the tumor is not diffuse in the breast and can be completely excised with negative margins. Under these circumstances, no increased risk of breast recurrence has been seen in patients with invasive lobular carcinomas treated with conservative surgery and radiation.^{15,16,16a}

Patients with positive axillary nodes do not have an increased risk of breast recurrence when treated with conservative surgery and radiation.^{2,5,8,15,17-19} In contrast, in patients undergoing mastectomy, 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 or tamoxifen (or both) with radiation in these patients.

One histopathologic feature that for-

merly appeared to be associated with a high risk of breast cancer recurrence after conservative surgery and radiation is the presence of an extensive intraductal component. This entity was first described by the Joint Center for Radiation Therapy, which defined it as the simultaneous presence of DCIS comprising 25% or more of the primary invasive tumor and DCIS in the surrounding normal breast tissue.^{19a} 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 extensive intraductal component (EIC). 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%.^{5,19b,19c} The increased risk for breast recurrence in EIC-positive tumors appears to be related to the presence of a significant residual tumor burden after gross excision.

Holland et al,²⁰ in a serial subgross and correlated mammographic examination of 217 mastectomy specimens, noted that EIC-positive tumors were significantly more likely to have residual tumor and tumor at a greater distance from the primary than were EIC-negative tumors. The residual tumor was predominantly DCIS. Therefore, the clinical and mammographic extent of an EIC-positive tumor may significantly underestimate the pathologic extent.

The risk of breast recurrence in EIC-positive patients can be diminished by the use of wide surgical resections and the achievement of negative margins of resection. A recent report from the Joint Center for Radiation Therapy has confirmed that negative margins of resection diminish the risk of breast recurrence in EIC-positive tumors.²¹ Therefore, the presence of an extensive intraductal component is a pathologic indicator that the disease in the breast may be more extensive than is clinically appreciated.

Assessment of resection margins in these patients is important in determining treatment options. Patients with EIC-positive tumors in whom the initial margins of resection are positive should undergo reexcision. If the reexcision margins are negative, current information suggests that these patients are appropriate candidates for conservative surgery and radiation. If the reexcision margins remain positive, mastectomy is the preferred treatment.

The influence of the final resection margin on breast cancer recurrence rates varies. In most reported series, positive margins of resection have been associated with an increased risk of breast cancer recurrence, although the magnitude has varied considerably.^{5,7,9,11,21-23} The variation in these results may be related to the extent of the surgical resection for the primary tumor, the presence or absence of an extensive intraductal component, the definition of a positive margin, the number of margins that are positive, and the extent of the margin positivity.

In the Milan Cancer Institute Trial II,³ the breast cancer recurrence rate for patients with positive margins was 12% for those undergoing a quadrantectomy compared with 17% for those whose primary surgical procedure was tumorectomy.

Gage et al²¹ have defined focal microscopic involvement as involvement evident in three or fewer low-power fields and diffuse involvement as involvement evident in three or more low-power fields. The 5-year actuarial breast recurrence rate was 9% for patients with focally positive margins, 28% for those with more diffuse involvement, and 3% for those with negative margins.

In this series, positive margins of resection were associated with a small increased risk of breast recurrence in EIC-negative tumors (10% compared with 2% for negative margins); however, 42% of EIC-positive tumors with diffuse margin involvement recurred compared with

0% of those with negative margins.

Recent information suggests that the use of adjuvant systemic chemotherapy or tamoxifen (or both) may diminish the 5-year rate of breast cancer recurrence in patients with positive margins.²² However, adjuvant therapy appears to delay the interval to recurrence and may not diminish the long-term risk of a recurrence in these patients. The 10-year actuarial breast cancer recurrence rate for patients with positive margins has ranged from 14% to 16%^{7,9,10} compared with 6% to 9% in patients with negative margins of resection.

Ideally, negative margins of resection should be achieved before radiation therapy to diminish the risk of a breast cancer recurrence, especially in patients who will not be receiving adjuvant systemic therapy. The ultimate outcome of EIC-negative tumors with focal margin involvement remains to be determined. Presently, reexcision is recommended in patients whose initial margin of resection is unknown or positive.

PATHOLOGIC EVALUATION

The excised tissue should be submitted for pathologic examination with appropriate clinical history and specification of anatomic site, 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, 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 margins of excision are marked with India ink or another suitable technique so that the pathologist can determine whether tumor is present or absent at the margins.

The pathologist includes certain basic data in each surgical pathology consultation report because the data are

important prognostically or are needed for staging or therapy. The following features should be included in the surgical pathology consultation report for invasive carcinoma:

- How the specimen was received (e.g., number of pieces, fixative, orientation)

- Laterality and quadrant of the excised tissue and the type of procedure, as specified by the surgeon

- Measured size of the tumor (in three dimensions if possible)

 - Histologic type and grade

- Presence or absence of coexistent DCIS or an extensive intraductal component

- Presence or absence of peritumoral angiolymphatic invasion

- Presence or absence of gross or microscopic carcinoma (either invasive carcinoma or DCIS) at the margins of excision; if possible, the distance of the tumor or biopsy site from the margin should be stated

- Lymph node status, including the number of lymph nodes found in the specimen, the number of involved nodes, the size of the largest involved node, and the presence or absence of extension beyond the lymph node capsule

It is important to specify the presence of any special histologic type of invasive breast cancer (e.g., tubular, mucinous, papillary), most of which are considered low grade. All ordinary invasive carcinomas (ductal, not otherwise specified) 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 modification of the Bloom-Richardson scheme. This system evaluates degree of tubule formation, nuclear grade, and mitotic rate to determine an overall histologic score.

In contrast to DCIS, lobular carcinoma in situ (LCIS, lobular neoplasia) is an

incidental histologic finding that is considered a marker of increased risk for subsequent breast cancer rather than a malignant lesion requiring surgical excision. This increase in risk applies to both breasts and is probably lifelong. The relation between lobular carcinoma in situ and surgical margins is not important.

The assessment of surgical margins is arguably the most important aspect in the pathologic evaluation of breast tumor excision 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, usually, indicates a need for further surgery, such as reexcision of the tumor site.

Frozen-section preparations of tissue obtained from image-guided needle biopsies of nonpalpable lesions or from mammographically directed biopsies done for microcalcifications are strongly discouraged. Lesions such as atypical ductal hyperplasia, radial scar, and papillary proliferations may be difficult to interpret in frozen-section preparations, and small foci of DCIS or microinvasive carcinoma may be lost or rendered incapable of interpretation by freezing artifact. Usually, frozen sections should be prepared only when enough tissue is present that the final diagnosis will not be compromised and when the information is necessary for immediate therapeutic decisions.

The presence or absence of regional or distant metastasis must be confirmed microscopically when appropriate tissue is submitted for examination. The AJCC/UICC (American Joint Committee on Cancer/International Union Against Cancer) TNM classification is recommended for appropriate stage grouping.

Determination of estrogen and progesterone receptors is standard for invasive breast carcinomas. This can be done either by the traditional ligand-

binding assays performed on snap frozen tissue or by immunohistochemistry performed on routinely fixed tissue sections. The results of ancillary studies (such as steroid receptor analysis, DNA ploidy, proliferative rate, and so forth) are usually reported in an addendum or supplement to the surgical pathology report.

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 with those of 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. The following 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 influence the likelihood of survival, but it may affect the quality of life.

Psychological research comparing patient adaptation after mastectomy with that after 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.

ABSOLUTE AND RELATIVE CONTRAINDICATIONS

Some absolute and relative contraindications exist in the selection of patients for breast conservation treatment with radiation.

Absolute Contraindications

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.

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. A history of previous therapeutic irradiation to the breast region that, combined with the proposed treatment, would result in an excessively high total radiation dose to a significant volume is another absolute contraindication.

Finally, persistent positive margins after reasonable surgical attempts absolutely contraindicate breast-conservation treatment with radiation. The importance of a single focally positive microscopic margin needs further study and may not be an absolute contraindication.

Relative Contraindications

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 either an absolute contraindication. In contrast, rheumatoid arthritis is not a relative or an absolute contraindication.

Patients with multiple gross tumors in the same quadrant and indeterminate calcifications must be carefully assessed for suitability because studies in this area

are not definitive.

Tumor size is not an absolute contraindication to breast conservation treatment, although few reports have been published about treating patients with tumors larger 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.

Breast size can be a relative contraindication. Women with large or pendulous breasts can be treated by irradiation if reproducibility of patient set-up can be ensured and if 6-MV photon beam irradiation is technically possible to obtain adequate dose homogeneity.

NONMITIGATING FACTORS

Certain clinical and pathologic features 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, evaluating the breast for local recurrence is feasible. The changes associated with recurrence can be detected at an early stage by 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 the choice of treatment. Tumors in a superficial subareolar location occasionally may require the resection of the nipple-areolar complex so that negative margins can be achieved, but this does not affect outcome. The patient and her physician need to assess whether such a resection is preferable to mastectomy.

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-

or second-degree relatives with breast cancer does not differ from that seen in patients without a family history of breast cancer. Little is known about the risk of breast recurrence in patients with hereditary breast cancer, but currently this is not a contraindication to breast-conserving therapy. A high risk of systemic relapse is not a contraindication for breast conservation but is a determinant of the need for adjuvant therapy.

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 diagnostic biopsy or definitive local excision before radiation therapy. Failure to consider these goals at all stages may jeopardize conservation of the breast.

Usually, local anesthesia can be used for the biopsy. Frequently, local anesthesia also can be used for the definitive local excision, particularly when it is combined with intravenous sedation in selected patients.

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 (Fig. 1). However, in the mid-inner aspect of the breast and 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 are inappropriate for lesions in the pe-

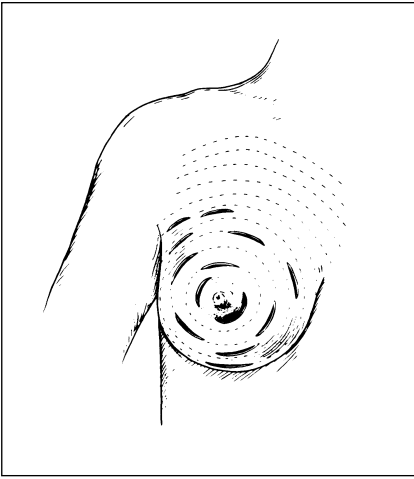


Fig. 1. Recommended location of incisions for performing breast biopsy. For larger lesions in the lower breast, particularly when skin must be excised, a radial incision often results in better cosmesis. Reproduced with permission from Souba and Bland.⁴⁵

riphery of the breast.

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.

BREAST TISSUE MANAGEMENT

The primary lesion should be excised with a rim of grossly normal tissue, avoiding excessive sacrifice of breast tissue. Tumors in the subareolar area may require excision of the nipple-areolar complex to ensure 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 cosmet-

ic result with nipple-areolar sacrifice is less than optimal.

The surgeon should approach lesions within the substance of the breast 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 critically important. Hematoma formation produces changes that are difficult to interpret by physical examination. In addition, the evolving scar from a hematoma makes interpretation of mammography 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.

The surgeon must orient the specimen with the use of sutures, clips, multi-colored indelible ink, or another suitable technique. The specimen should not be sectioned before it is submitted to the pathologist. 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.

The specimen should be examined for the determination of a grossly clear margin. If a clear margin is not evident, the tumor should be reexcised at that time. Routine frozen-section evaluation of margins is optional and does not guarantee negative margins after a complete examination.

IMAGE-DIRECTED SURGERY

Nonpalpable carcinoma may be diagnosed by image-directed biopsy or needle localization and excision. If a patient has a nonpalpable carcinoma diagnosed by image-guided biopsy, breast-conserving

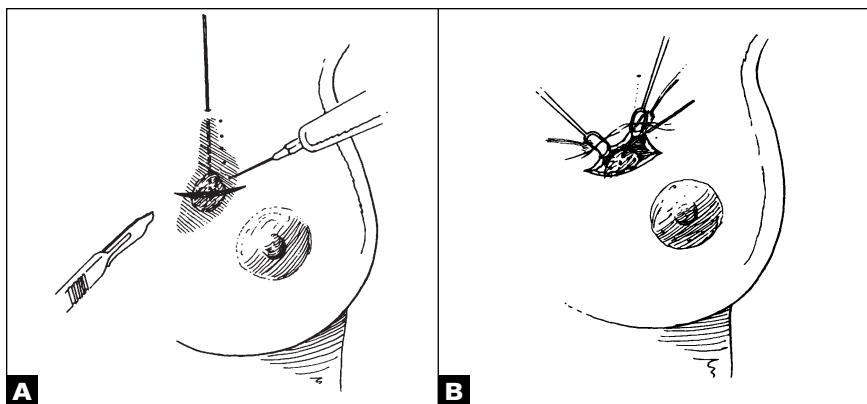


Fig. 2. (A) For needle localization biopsy, the incision should be placed over the lesion, not at the point of entry of the wire into the breast. (B) The breast tissue is dissected until the wire is identified within the parenchyma, then the wire is stabilized distally and brought into the field. Traction on the wire should be avoided always. Reproduced with permission from Silen et al.⁴⁶

surgery should be conducted with presurgical localization with a guide such as guide wire.

Suspicious lesions detected by mammography require presurgical localization to ensure accurate removal of the abnormal area and to avoid excess sacrifice of breast tissue. The method of localization may be needle-hook wire, Evans 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 to achieve the best cosmetic result. Tunneling should be avoided, and the surgeon should attempt to make the skin incision as close to the lesion as possible (Fig. 2). The principles of skin incision and breast tissue management that were discussed earlier should apply.

Localization titanium clips may be

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

SPECIMEN RADIOGRAPH

A radiograph of the specimen should be obtained, preferably in two dimensions (orthogonal projections). Magnification and compression of the specimen increase the resolution of the radiograph.

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 before the excision site is closed 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.

REEXCISION OF BIOPSY SITE

The surgeon must reexcise the previous biopsy site carefully to ensure negative margins of resection, to avoid excess breast tissue removal, and to achieve good cosmesis. Proper orientation of the original biopsy specimen avoids removal of an already adequate margin. When the site of inadequate margins is not known, a rim of tissue must be removed around the previous biopsy site. A small segment of skin incorporating the biopsy site should be removed, and undermining should be kept to a minimum.

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

AXILLARY DISSECTION

The breast incision and the axillary incision should be separate. A continuous dissection from the breast into the axilla is likely to produce unsightly deformities. The exception may be an axillary tail tumor that can be readily removed through the axillary incision. A transverse incision low in the axilla that stops at the posterior border of the pectoralis major muscle produces an excellent cosmetic result and good exposure. A linear incision posterior and parallel to the edge of the pectoralis major also provides good exposure and a cosmetically acceptable scar.

For invasive tumors that are 1 cm or smaller in diameter and tumors of a favorable histologic type (i.e., tubular, mucinous, papillary), removal of level I nodes is adequate. For staging purposes, removal of level I and level II nodes permits an accurate assessment of axillary nodal status.

Removal of level III nodes is advised only when encompassing obvious disease is necessary. Sentinel node lymphatic mapping is still considered investigational.

The thoracodorsal and long thoracic nerves should be preserved. The medial pectoral nerve also should be preserved. Preservation of the intercostal brachial nerve is desirable, but it may not be possible if preservation compromises adequate excision of grossly positive or suspicious nodes. Circumferential stripping of the axillary vein is unnecessary and may increase the incidence of edema.

Closed suction drainage is advisable.

Exercise may be prescribed early in the postoperative period. Early postoperative exercise may prolong axillary drainage, but it prevents frozen shoulder. Shoulder immobilization with arm slings and wraps should be avoided.

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.

ELEMENTS IN THE TECHNIQUE OF IRRADIATION

A consensus exists regarding some but

not all of the elements in the technique of irradiation. Treatment facilities should conform to American College of Radiology 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 after uncomplicated breast-conserving surgery.

The radiation oncologist should use measures to ensure reproducibility of patient set-up, treatment simulation, treatment planning, and choice of super-voltage equipment to ensure dose homogeneity. High-energy photons (10 MV or more) may be indicated for very large-breasted women or patients who have significant dose inhomogeneity with treatment 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 shown. Currently, three-dimensional dose distributions are not considered standard.

Each field should be treated on a daily basis, Monday through Friday. A bolus should not be used. To reduce the risk of radiation pneumonitis, not more than 3.0 to 3.5 cm of lung (as projected on the beam radiograph at isocenter) ordinarily should be treated, and a minimum of 1.0 to 1.5 cm of lung is required. For left-sided lesions, efforts should be made to reduce 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.

Controversy exists about the need for delivering an additional boost dose to the primary site. Several considerations may be involved in the decision to use a

boost. Histologic studies show that residual cancer after resection of the primary is usually near the primary site, and recurrences after treatment usually are seen at or near the primary site. Boost treatment can be delivered without significant morbidity.

Although boost irradiation generally is used, the precise indications for its use are not well defined. Research indicates, however, 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 in which 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.

TECHNIQUES TO BE AVOIDED

Although no consensus exists about the advisability of treating nodal areas with irradiation, agreement does exist about the need to avoid certain radiation therapy techniques for the treatment of regional lymph nodes.

Axillary irradiation is usually unnecessary after a complete axillary dissection (levels I to III). Irradiation of the supraclavicular fossa and the contiguous apical region may be considered if a large number of lymph nodes (four or more) con-

tain tumor. The benefit of radiation in patients with one to three positive nodes is unknown.

Overlap between adjacent fields should be avoided.

Follow-up Care

Follow-up assessment of the results of breast-conservation treatment emphasizes the cosmetic outcome and 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 when indicated
3. Providing the individual practice with the database necessary to optimize treatment and compare outcomes with national standards

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

The evaluations that the physician should perform and the intervals after the completion of treatment when they should be done are described in the remainder of this section.

PHYSICAL EXAMINATION

Local failure occurs at a constant rate in the time interval; therefore, frequency of examination should be based on risk factors for both local and distant recurrence. The intervals for examination are as follows:

Every 3 to 6 months, years 1 to 3. This interval varies for patients receiving adjuvant chemotherapy, who need more frequent assessment during their active treatment.

Every 6 months, years 4 and 5. Some

investigators prefer to continue semianual examinations through year 8 because the rate of local recurrence is constant through that time interval.

Annually after year 5. More frequent follow-up may be needed for patients at exceptionally high risk.

MAMMOGRAPHY

A goal of follow-up imaging of the treated breast is the early recognition of tumor recurrence. Postoperative and irradiation changes overlap with signs of malignancy on a mammogram; health professionals should know this so they can avoid unnecessary biopsy. The changes include masses (postoperative fluid collections and scarring), edema, skin thickening, and calcifications.

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

For accurate interpretation of mammograms and assessment of the direction of change, the current mammogram must be compared in sequence with 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 to quantitate them. In some cases, a view with the x-ray beam tangential to the scar and other oblique views help to differentiate recurrent tumor from postoperative changes.

Ultrasonography can characterize a postoperative mass, such as a seroma, as

Table 10
Four-Point Scoring System of Breast Cosmesis

Excellent	Treated breast almost identical to untreated breast
Good	Minimal difference between treated breast and untreated breast
Fair	Obvious difference between treated breast and untreated breast
Poor	Major functional and esthetic sequelae in treated breast

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 facilitate more confident radiographic interpretations.

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 should be performed for comparison 3 to 9 months after tumor excision and completion of all therapies.

Thereafter mammography should be done at least annually or at more frequent intervals as warranted by clinical or radiographic findings.

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 approxi-

mately the same for both the treated and the untreated breast.)

OTHER TESTS

Symptomatic patients are justifiably evaluated with other medical tests (e.g., radionuclide bone scan, chest radiography, computerized tomography [CT] scans, liver function tests) as indicated by the character of their medical problem. An annual chest radiograph may be appropriate in patients who smoke. Randomized controlled trials have shown that routine use of these tests provides no benefit for asymptomatic patients with stage I or II breast carcinoma. No survival benefits have been shown, and the cost-effectiveness of using such procedures in routine follow-up is seriously in question.²⁴

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 the following:

1. Assessment of the overall cosmetic result. A 4-point scoring system is recommended for assessing the cosmetic result (Table 10).

2. Assessment of complications. Complications should be specified with regard to symptomatology and physical findings. The use of the RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) Radiation Toxicity

Scoring Scheme is recommended for the grading of complications.¹ 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.

Areas for Further Research

Although great progress has been made in the treatment of early-stage breast cancer, several important questions remain unresolved. Clinical and laboratory investigations will address many of the follow-

ing questions in the coming years:

1. What is the significance of involvement of the pathologic margins of resection, and how are those margins defined?

2. Can breast irradiation be omitted after breast-conserving surgery in some patients?


3. What is the optimal integration of radiation and chemotherapy?

4. What is the role of preoperative chemotherapy in larger tumors?

5. When should regional nodal irradiation be used?

6. How will genetic considerations influence patient selection?

7. What is the role of sentinel node mapping?

8. What is the appropriate frequency of follow-up mammography of the treated breast? 

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REVIEW AND SUMMARY OF THE LITERATURE

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