Breast cancer is the most common cancer among women and the second leading cause of cancer-related death overall. One in eight women will be diagnosed with breast cancer in the course of her lifetime. Generally, patients with breast cancer present in one of three ways: with a palpable breast mass, with a change in the skin of the breast or the nipple, or with an abnormal mammogram. As is the case for patients with benign breast complaints [see 3:9 Benign Breast Disease], the evaluation begins with a thorough history and a careful physical examination.

Clinical Evaluation

HISTORY

A complete medical history should be obtained, including current medications, allergies, tobacco and alcohol use, previous surgical procedures, medical problems, and a brief social history. Special attention should be paid to the duration of the symptoms and the changes that took place over time. It is important to determine whether there have been any previous breast problems; if breast biopsies were performed earlier, the pathologic findings of these biopsies should be obtained.

A thorough search for risk factors for breast cancer [see 3:9 Benign Breast Disease] should be undertaken, though the absence of these risk factors does not exclude the presence of breast cancer. An accurate and complete family history is essential for quantifying a woman’s genetic predisposition to breast cancer. Approximately 5% to 10% of breast cancers are hereditary. Questions about breast cancer in family members should go back several generations and should extend to third-degree relatives, with age at diagnosis recorded if available. Similarly, any family history of ovarian or other cancers (particularly those that developed when the relative was young) should be recorded, along with age at diagnosis. Any personal history of cancer should be recorded, with particular attention paid to breast, ovarian, and endometrial cancers. Previous exposure to radiation, especially in the area of the chest wall, should be noted. Admittedly, it is not always possible to obtain complete and precise family history data, whether because of time constraints or because of family issues (e.g., premature deaths, small family size, or distant or broken families).

PHYSICAL EXAMINATION

The physical examination begins with inspection of the breasts for asymmetry, skin or nipple changes, nipple retraction, erythema, or peau d’orange (orange-peel appearance). Skin dimpling, which can be indicative of an underlying mass lesion, can be accentuated by having the patient sit with her hands pushing against her hips to contract the pectoral muscles. Each breast should then be carefully palpated from the clavicle to below the inframammary fold and from the sternum to the posterior axillary line, with careful attention to the subareolar area. This is done with the patient both supine and sitting. If an abnormal area is identified, its location, size, consistency, contour, tenderness, and mobility should be described. Certain physical findings, such as skin changes, irregular borders, firmness, irregular margins, and immobility, are associated with a greater likelihood of cancer, though their absence does not exclude the diagnosis. The lymph nodes in the supraclavicular, infraclavicular, and axillary basins should be thoroughly examined, and any enlargement should be noted. The size, mobility, and number of enlarged nodes should be recorded, as should matting of nodes or fixation of nodes to the chest wall.

Investigative Studies

IMAGING

Mammography

Diagnostic mammography is the first imaging study employed to evaluate breast abnormalities. It differs from screening mammography in that it is performed when a breast abnormality is already present; it is a more comprehensive examination and consists of multiple specialized images (e.g., magnification views or spot compression views). Diagnostic mammography includes a mammogram of the contralateral breast to rule out synchronous, nonpalpable lesions whenever a woman older than 35 years presents with a palpable breast mass or other specific symptoms. Approximately 4% to 5% of breast cancers occur in women younger than 40 years, and about 25% occur in women younger than 50 years.

Mammography fails to detect 10% to 15% of all palpable malignant lesions, and its sensitivity is particularly decreased in women with lobular carcinoma or radiographically dense breast tissue. Such patients may benefit from digital mammography, which is not more effective than traditional mammography in the general population but which seems to be more effective in the subset of patients with dense breast tissue. Because of the limitations of diagnostic mammography, a negative mammogram should not influence the decision to perform a biopsy of a clinically palpable lesion. The purpose of mammography in this setting is to look for synchronous lesions or nonpalpable calcifications surrounding the palpable abnormality, not to determine whether biopsy of the palpable abnormality is indicated.

Ultrasonography

The main value of ultrasonography lies in its ability to distinguish cystic from solid lesions. It is also very useful for directing fine-needle aspiration (FNA) or core-needle biopsy (CNB): it permits real-time manipulation of the needle and direct confirmation of the position of the needle within the lesion. It has also been used to guide the performance of investigational tumor-ablating techniques [see 3:5 Breast Procedures].

Magnetic Resonance Imaging

Magnetic resonance imaging after injection of gadolinium contrast enhances many malignant lesions in relation to normal breast
Patient has ductal carcinoma in situ (DCIS)

Treatment depends on extent of disease.

Patient has early-stage invasive breast cancer (stage I or II)

Treatment choices are
- Lumpectomy, SLNB, and radiation
- Total mastectomy and SLNB

Choice depends on patient preference and on presence or absence of any contraindications to limited surgery with radiation.

Patient undergoes mastectomy

Look for positive nodes.

SLNB is negative

If primary tumor is < 1 cm, follow up.
If primary tumor is ≥ 1 cm, administer adjuvant chemotherapy and/or hormone therapy if tumor is estrogen receptor (ER) positive. Then, if tumor is > 5 cm, irradiate chest wall and follow up; if tumor is ≥ 1 cm but ≤ 5 cm, follow up.

SLNB is positive

Perform complete lymph node dissection.

Nodes are unfavorable, there are > 4 positive nodes, or there is extracapsular extension

Administer adjuvant chemotherapy (hormone therapy if patient is postmenopausal).

Mastectomy patients

Irradiate chest wall and axilla and follow up.

Limited surgery patients

Irradiate breast and axilla and follow up.

DCIS is not extensive

Treatment choices are
- Simple mastectomy ± reconstruction
- Wide excision

Patient undergoes simple mastectomy ± reconstruction

Consider SLN biopsy.

DCIS is extensive

Perform simple mastectomy ± reconstruction. Consider SLN biopsy.

Patient undergoes wide excision

Assess margin status.

Margins are positive

Treatment choices are
- Reexcision to negative margins and radiation therapy
- Simple mastectomy ± reconstruction

Margins are negative

Irradiate breast and follow up, or follow up only.
Patient has breast cancer
Management depends on clinical stage.

Patient has locally advanced breast cancer (stage III or inflammatory carcinoma)
Perform needle or incisional biopsy to obtain tissue diagnosis and hormone receptor data. Administer “neoadjuvant” chemotherapy. Restage to identify distant metastases.

Patient has distant metastases (stage IV)
Determine whether patient is eligible for therapy on protocol. Consider radiation therapy to relieve pain from bone marrow metastases or avert pathologic fracture at metastatic site. Consider “toilet mastectomy” if patient has locally advanced and ulcerated primary tumor that hinders administration of chemotherapy.

Patient undergoes lumpectomy
If clean margins are not obtained, perform mastectomy (see left). If clean margins are obtained, look for positive nodes.

Limited surgery patients
Irradiate breast and follow up.

SLNB is negative
Administer radiation therapy. If primary tumor < 1 cm, follow up. If primary tumor ≥ 1 cm, administer adjuvant chemotherapy and/or hormone therapy if tumor is ER positive and follow up. (Note: chemotherapy may precede radiation therapy.)

Tumor is inoperable
Administer a different chemotherapy or hormone therapy regimen. Restage to assess operability.

No metastases are identified on restaging
Determine whether tumor is operable.

Metastases are identified on restaging
Initiate appropriate management.

Tumor is operable
Perform modified radical mastectomy. Lumpectomy with axillary dissection is an option for some patients. Consider radiation to chest wall and axilla. (Most patients require both surgery and radiation in addition to chemotherapy.) Follow up.

SLNB is negative
Administer radiation therapy. If primary tumor < 1 cm, follow up. If primary tumor ≥ 1 cm, administer adjuvant chemotherapy and/or hormone therapy if tumor is ER positive and follow up.

Patient is ineligible for therapy on protocol
Initiate palliative chemotherapy or hormone therapy.

Patient is eligible for therapy on protocol
Initiate therapy on protocol.
parenchyma. Although some benign lesions (e.g., fibroadenomas) are also enhanced by gadolinium, the contrast agent appears to enhance malignant lesions more rapidly and often to a greater extent.

The sensitivity and specificity of MRI in distinguishing benign from malignant lesions are still being assessed. The main approved use of MRI in breast disease is for identification of leaks in silicone breast implants, because MRI can detect the ruptured silicone membrane within the silicone gel. MRI is also useful in identifying occult primary tumors in women who have palpable axillary nodes but no palpable or mammographically identified primary breast lesion. MRI appears to be effective for assessing the extent of vaguely defined tumors, identifying unsuspected multifocal disease, and helping identify patients who are not eligible for breast-conserving surgery. In addition, it appears that MRI can distinguish between a locally recurrent tumor and surgical scarring or radiation-induced change after lumpectomy and radiation, though the technology may not provide reliable readings until 18 months or more after surgery or the completion of radiation therapy. MRI can also detect contralateral breast cancer that was missed by clinical breast examination and mammography at the time of breast cancer diagnosis in approximately 3% of cases. To date, however, MRI has not been incorporated into the standard algorithms for the evaluation of breast cancer patients; most authorities recommend that it be employed selectively.

Other Modalities

Nuclear medicine studies, such as sestamibi scintimammography and positron emission tomography (PET), remain primarily investigational tools. At present, there is no proven role for thermography or xerography in the evaluation of breast problems.

BIOPSY

Whenever possible, biopsies should be performed percutaneously. If the lesion is palpable, either FNA biopsy or CNB is suitable [see 3:5 Breast Procedures]. FNA biopsy is less invasive, but its performance requires the specialized expertise of a cytopathologist. CNB has the advantage of allowing histologic evaluation, which permits invasive cancers to be distinguished from in situ cancers and facilitates receptor analysis. If the lesion is not palpable, biopsy can be performed under the guidance of diagnostic imaging. Stereotactic and ultrasound-guided percutaneous core biopsy techniques are minimally invasive and more expedient than open biopsy. With any of the imaging-guided approaches, however, it is important to verify that the visual interpretation of the imaging abnormality is in concordance with the pathologic analysis of the specimen.

Management

STAGING

In patients with newly diagnosed breast cancer, it is important to determine the overall extent of disease before embarking on definitive therapy. This process, referred to as clinical staging, includes (1) physical examination to identify any areas of palpable disease in the breasts or the axillary and supraclavicular nodes, along with a detailed clinical history to identify symptoms that may suggest metastatic disease; (2) imaging studies, including mammography, chest x-ray, and sometimes bone scans or CT scans of the chest, the abdomen, or the head; and (3) laboratory studies, including a complete blood count (CBC) and liver function tests.

The extent of preoperative staging should be guided by the size and other characteristics of the primary tumor and by the patient's history and physical examination. The majority of patients with breast cancer present with early-stage disease and a low probability of metastatic disease; therefore, extensive testing adds cost without offering much benefit. For patients with stage I or II disease, mammography and routine preoperative blood work should be performed before definitive surgical therapy is initiated; further imaging studies should be reserved for patients who have abnormal test results or clinical symptoms that suggest metastatic disease (e.g., bone pain). For patients with higher-stage disease at presentation, the use of additional staging studies should be guided by the patient's clinical situation.

Changes in American Joint Committee on Cancer Breast Cancer Staging System

A number of evidence-based changes to the sixth edition of the American Joint Committee on Cancer (AJCC) TNM staging system for breast cancer were adopted for use in tumor registries in January 2003 [see Tables 1 and 2]. These changes reflected growing use of sentinel lymph node biopsy (SLNB) and of immunohistochemical and molecular technologies to detect nodal metastases. They also included quantitative criteria for distinguishing micrometastases from isolated tumor cells and specific identifiers for recording the use of SLNB, immunohistochemical staining, and molecular biologic techniques. In addition, the classification of lymph node status was modified to include the number of affected axillary lymph nodes, and changes were made to the classification of level III axillary lymph nodes and lymph nodes outside the axilla. These modifications of the AJCC staging system should bring standardization to the collection of important clinical-pathologic information.

NONINVASIVE CANCER

Ductal Carcinoma in Situ

Before mammographic screening was widely practiced, ductal carcinoma in situ (DCIS) was generally identified either as a palpable lesion (usually with comedo histology) or as an incidental finding on a biopsy performed for another lesion. With the increasing use of mammography, DCIS is accounting for a growing proportion of breast cancer cases. According to the Surveillance Epidemiology and End Results (SEER) database, 15.9% of newly diagnosed breast cancers between 1997 and 2000 were DCIS.

It was recognized early on that DCIS had a very favorable prognosis compared with other forms of breast cancer: long-term survival approached 100% after treatment with mastectomy. Axillary lymph nodes were positive in only 1% to 2% of patients, most of whom had large or palpable lesions or comedo histology. The prognosis for DCIS continues to be very favorable in relation to that for invasive breast cancers. In theory, there is no potential for metastatic disease with a purely in situ lesion. In practice, however, axillary node metastases continue to be found in 1% to 2% of patients thought to have pure DCIS, presumably arising from a small area of invasion that was missed on pathologic evaluation.

DCIS is believed to be a true anatomic precursor of invasive
breast cancer. There are at least two lines of evidence that support this conclusion. First, when DCIS is treated with biopsy alone (usually because it was missed on the initial biopsy and not found until subsequent review), invasive carcinoma develops in 25% to 50% of patients at the site of the initial biopsy; all these tumors appear within 10 years and are of ductal histology. Second, when DCIS recurs locally after breast conservation, invasive ductal carcinoma appears in about 50% of patients. The

<table>
<thead>
<tr>
<th>Table 1</th>
<th>American Joint Committee on Cancer TNM Clinical Classification of Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget disease of nipple with no associated tumor*</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 2.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T1mic</td>
<td>Microinvasion ≤ 0.1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor &gt; 0.1 cm but ≤ 0.5 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 0.5 cm but ≤ 1.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt; 1.0 cm but ≤ 2.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 2.0 cm but ≤ 5.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 5.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to (a) chest wall or (b) skin</td>
</tr>
<tr>
<td>T4a</td>
<td>Extension to chest wall</td>
</tr>
<tr>
<td>T4b</td>
<td>Edema (including peau d’orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast</td>
</tr>
<tr>
<td>T4c</td>
<td>Both of the above (T4a and T4b)</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma‡</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed (e.g., previously removed)</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis to movable ipsilateral axillary lymph node(s)</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in 1–3 axillary lymph nodes (at least 1 tumor deposit &gt; 2.0 mm)</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in clinically apparent axillary lymph nodes in the absence of axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in 10 or more axillary lymph nodes or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in 10 or more axillary lymph nodes (at least 1 tumor deposit &gt; 2.0 mm) or in infraclavicular lymph nodes</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent</td>
</tr>
<tr>
<td>N3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)</td>
</tr>
</tbody>
</table>

* Paget disease associated with a tumor is classified according to the size of the tumor.
† The chest wall includes ribs, the intercostal muscles, and the serratus anterior, but not the pectoral muscle.
‡ Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically, there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is attributable to tumor embolization of dermal lymphatics with engorgement of superficial capillaries.
SLN—sentinel lymph node IHC—immunohistochemistry RT-PCR—reverse transcriptase polymerase chain reaction
true relationship between DCIS and invasive ductal carcinoma awaits a better understanding of the molecular biology of breast cancer development.

The consequence of the view that DCIS is a precursor of invasive cancer is that treatment is required once the diagnosis is made. Treatment options for DCIS include mastectomy and breast conservation, consisting of partial mastectomy followed by radiation; however, it should be remembered that although the risk of local recurrence is greater after breast conservation for DCIS than after mastectomy, the likelihood of metastatic disease is very small. Wide excision to microscopically clean margins followed by radiation therapy has become an accepted alternative to mastectomy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study, which examined the role of radiation in the treatment of DCIS, found that the addition of radiation therapy to wide excision reduced the recurrence rate at 43 months after operation by approximately half, from 16.4% with wide excision alone to 7.0% with wide excision and radiation. The report also suggested that the addition of radiation therapy might reduce the incidence of invasive recurrences. Partial-breast irradiation is now being studied as an alternative to whole-breast irradiation. To date, the results have been generally favorable, though the follow-up periods have been short. Smaller areas of DCIS, particularly those that are of low to intermediate nuclear grade and are excised with wide margins, are increasingly being treated without radiation. Omission of radiation therapy is a complex decision that should be based on the patient’s histology, the presence or absence of other risk factors, the presence or absence of contraindications to radiation therapy, and the degree to which the patient is willing to accept a higher local recurrence rate. This option is probably best pursued in the context of a clinical trial. If clean margins cannot be obtained or if the cosmetic result is expected to be poor after excision to clean margins, mastectomy should be performed.

Most patients in whom DCIS is identified mammographically can choose between mastectomy and wide excision with or without radiation, either of which yields excellent long-term survival. Given the lack of any significant difference in survival between the two options, the patient must weigh her feelings about the risk of a local, possibly invasive, recurrence after breast conservation against her feelings about the cosmetic and psychological effects of mastectomy. Mastectomy remains a reasonable treatment even for patients with very small DCIS lesions if the primary concern is to maximize local control of the cancer. Breast reconstruction after mastectomy for DCIS is an option that is open to most such patients.

SLNB [see 3:6 Lymphatic Mapping and Sentinel Lymph Node Biopsy] usually is not required for the management of DCIS but should be considered in certain high-risk DCIS patients. It is generally offered to patients with palpable DCIS because of the high risk of invasive carcinoma associated with this condition. It is also offered to patients scheduled to undergo mastectomy for DCIS, the rationale being that if invasive carcinoma is detected at the time of mastectomy, SLNB would be impossible and a full axillary node dissection would be required. Some surgeons offer SLNB to patients with high-grade DCIS, particularly if comedonecrosis is present, but this measure is optional if breast conservation is planned.

There are certain patients with DCIS for whom mastectomy remains the preferred treatment, such as those who have lesions larger than 5 cm in diameter or extensive microcalcifications on mammography. Some surgeons would also include in this category those who have comedo lesions larger than 2.5 cm and those who present with palpable DCIS. In these patients, the local recurrence rate after breast conservation, even in conjunction with radiation therapy, remains high. As many as half of these recurrences will contain invasive cancer with metastatic potential.

**INVASIVE CANCER**

Invasive breast cancer is the most common malignancy affecting women. Most breast malignancies arise from the terminal duct–lobular unit. The majority are of ductal histology, and a small proportion (10% to 15%) are of lobular histology. The histologic type makes no difference to treatment, which is based on clinical staging and various patient factors. Lobular carcinomas can be challenging both diagnostically and therapeutically. In particular, they may be difficult to identify because they are often mammographically occult and tend to have an insidious growth pattern, infiltrating into the surrounding breast parenchyma. Special subtypes of ductal carcinoma have also been described. One such subtype is tubular carcinoma, which represents about 3% to 5% of all invasive carcinomas. Pure tubular carcinomas are associated with a significantly better prognosis, and distant metastasis is highly unlikely. Mucinous, or colloid, carcinoma is also associated with an excellent prognosis when diagnosed in its pure form. Medullary carcinoma, a subtype common in women with a hereditary predisposition to breast cancer, is associated with a more favorable prognosis as well.

Evaluation of newly diagnosed breast cancers should also include determination of estrogen receptor (ER) and progesterone receptor (PR) status and assessment of HER-2/neu amplification.

**TREATMENT OPTIONS**

**Mastectomy versus Limited Surgery**

Several randomized prospective studies have documented that segmental resection (lumpectomy), axillary dissection, and postoperative irradiation of an intact breast result in overall survival...
rates equal to those of modified radical mastectomy.\textsuperscript{13-16} Although most women with stage I and II breast cancers—indeed, most women with breast cancer—are candidates for breast conservation therapy [see Table 3], some still require or desire mastectomy. When a patient is eligible for limited surgery, the decision between mastectomy and breast conservation with radiation therapy is made on the basis of patient and physician preference, access or lack of access to radiation therapy, and the presence or absence of contraindications to breast conservation.

Patients undergoing lumpectomy and radiation therapy are at risk for local recurrence in the treated breast, as well as for the development of a new primary tumor in the remaining breast tissue. Local recurrences can generally be managed with mastectomy; overall survival is equivalent to that of women who underwent mastectomy at the time of initial diagnosis. There may, however, be a significant cost to the patient in terms of anxiety about recurrence, as well as the morbidity and potential mortality associated with undergoing a second surgical procedure.

On the other hand, patients who choose mastectomy as their initial surgical treatment face the psychological consequences of losing a breast. Although they are at lower risk for local recurrence than patients who choose lumpectomy, axillary node dissection, and radiation, their overall survival does not seem to be significantly improved. Each physician and each patient must weigh the inconvenience and potential complications of radiation therapy and the risk of local recurrence against the value of breast preservation, keeping in mind that the choice between procedures appears to have no significant effect on survival.

**Contraindications to breast conservation** Patients for whom mastectomy is still clearly the treatment of choice fall into four broad categories: (1) those in whom radiation therapy is contraindicated, (2) those in whom lumpectomy would have an unacceptable cosmetic result, (3) those for whom local recurrence is a concern, and (4) those high-risk patients in whom surgical prophylaxis is appropriate.

Radiation therapy may be contraindicated for any of several reasons. Some patients choose not to undergo radiation therapy, either because it is inconvenient or because they are concerned about potential complications (including the induction of second malignancies). Some patients simply do not have access to radiation therapy, either because they live in a rural area or because they have physical conditions that make daily trips for therapy onerous. Time and travel issues related to weeks-long courses of conventional radiotherapy have led to studies investigating partial-breast or limited-field irradiation after breast-conserving surgery.\textsuperscript{17} Other patients have medical or psychiatric disorders that would make it extremely difficult for them to comply with the daily treatment schedule. Still others have specific medical contraindications to radiation therapy, including pregnancy, collagen vascular disease, or previous irradiation of the chest wall (as in a woman with a local recurrence of a breast carcinoma that was treated with radiation therapy). Although there are some clinical data supporting the use of repeat local excision without further irradiation to treat local recurrence after radiation therapy, most authorities favor mastectomy.\textsuperscript{18} Prospective, randomized trials have been initiated to determine the safety of partial-breast irradiation, and the 66-month follow-up data currently available suggest that partial-breast irradiation does not differ significantly from whole-breast radiation with respect to local recurrence risk and yields better cosmetic results.\textsuperscript{19}

When resection of the primary tumor to clean margins would render the appearance of the remaining breast tissue cosmetically unacceptable, mastectomy may be preferable. This is likely to be the case, for example, in patients with large primary tumors relative to their breast size: resection of the primary tumor would remove a substantial portion of the breast tissue. Another example is patients with multiple primary tumors, who would have not only an increased risk of local recurrence but also poor cosmetic results after multiple wide excisions. Patients with superficial central lesions, including Paget disease, are eligible for wide excision (including the nipple and the areola) followed by radiation therapy, provided that clean margins are obtained. The survival and local recurrence rates in these patients are equivalent to those in other groups of patients undergoing lumpectomy and radiation.\textsuperscript{20-22} In many cases, the cosmetic results of this procedure are preferable to those of immediate reconstruction, and there is always the option to reconstruct the nipple and areola later.

Patients who are at high risk for local recurrence often choose mastectomy as primary therapy. Features of primary tumors that are associated with higher local recurrence rates after limited surgery and irradiation include gross residual disease after lumpectomy, multiple primary tumors within the breast, an extensive intraductal component, large tumor size, lymphatic vessel invasion, and lobular histologic findings.\textsuperscript{23}

In practice, obtaining tumor-free margins is probably the most critical factor in decreasing the risk of local recurrence. The difficulty of obtaining microscopically clean margins in tumors with an extensive intraductal component and in lobular carcinomas may account for the higher local recurrence rates sometimes seen with these tumors. Histologic analysis of mastectomy specimens from patients with tumors with an extensive intraductal component has shown a high rate of multifocality within ipsilateral breast tissue; this residual disease is thought to be the nidus for local recurrence.\textsuperscript{24}

The long-term benefits of choosing mastectomy to reduce local recurrences are not clear. Whereas the appearance of distant metastases typically heralds incurable and ultimately fatal disease, local recurrence after breast conservation appears to have little, if any, impact on overall survival. Prospective, randomized trials have had difficulty showing a statistically significant reduction in survival in women who have had a local recurrence after limited surgery and radiation therapy. It has been suggested that additional follow-up may eventually confirm reduced survival in some patients with local recurrences. Still, most of the evidence suggests that local recurrences are not the source of subsequent distant metastases. It is worthwhile to keep in mind, however, that even if mastectomy to prevent local recurrence does not actually improve survival, it may nevertheless provide significant benefit by reduc-

### Table 3 Determinants of Patient Eligibility for Lumpectomy and Radiation Therapy

<table>
<thead>
<tr>
<th>Primary tumor ≤ 5 cm (may be larger in selected cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor of lobular or ductal histology</td>
</tr>
<tr>
<td>Any location of primary within breast if lumpectomy to clean margins (including central lesions) will yield acceptable cosmetic results</td>
</tr>
<tr>
<td>Clinically suspsicious but mobile axillary nodes</td>
</tr>
<tr>
<td>Tumor either positive or negative for estrogen and progesterone receptors</td>
</tr>
<tr>
<td>Any patient age</td>
</tr>
<tr>
<td>Absence of contraindication to radiation therapy (e.g., previous radiation therapy to breast or severe collagen vascular disease, such as scleroderma)</td>
</tr>
</tbody>
</table>
Options for axillary staging  The histologic status of the axillary nodes is the single most important predictor of outcome for breast cancer. Traditionally, axillary dissection has been a routine part of the management of breast cancer. It has been used to guide subsequent adjuvant therapy and provide local control, and it may have contributed a small overall benefit in terms of survival. Unfortunately, axillary dissection can be associated with sensory morbidities and lymphedema.

SLNB is a minimally invasive, less morbid, and quite accurate method of detecting or ruling out occult lymph node metastasis. SLNB is based on the principle that the sentinel lymph node (SLN) is the first node to which the tumor spreads; thus, if the SLN is tumor free, the patient can be spared the morbidity of an axillary dissection. SLN biopsy identifies an increased number of patients with micrometastases, with some identified by immunohistochemical staining alone. Treatment of patients who have only micrometastases to axillary nodes remains a topic of debate. Unfortunately, the clinical trial of SLNB that the American College of Surgeons Oncology Group initiated in an attempt to address this question (ACOSOG Z11) closed because of lack of accrual.

Breast reconstruction after mastectomy  Advances in reconstructive techniques have made breast reconstruction increasingly popular. Breast reconstruction may be done either at the time of the mastectomy (immediate reconstruction) or later (delayed reconstruction). In the past, reconstruction was generally delayed for 1 to 2 years after mastectomy; now, it is most often performed immediately after mastectomy. In general, however, immediate reconstruction is not ideal for patients likely to require postoperative adjuvant therapy. Although it can still be done in these circumstances, the cosmetic outcome may be inferior because irradiation can produce capsular contracture in patients undergoing prosthetic reconstruction.

Prosthetic reconstruction involves the use of an implant to restore the breast contour. It is technically the simplest type of reconstruction but can still result in complications such as contracture, infection, and rupture, which may necessitate further surgery. Autologous reconstruction involves the transfer of the patient’s own tissue to reconstruct the breast. Tissue from various sites (e.g., the rectus abdominis and the latissimus dorsi) has been used for breast reconstruction. Skin-sparing mastectomy with immediate reconstruction consists of resection of the nipple-areola complex, any existing biopsy scar, and the breast parenchyma, followed by immediate reconstruction. The generous skin envelope that remains optimizes the cosmetic result after breast reconstruction. The procedure is oncologically safe and does not lead to an increase in the incidence of local recurrence.

Radiation Therapy  

Current radiation therapy regimens consist of the delivery of approximately 50 Gy to the whole breast at a dosage of approximately 2 Gy/day, along with, in most cases, the delivery of an additional 10 to 15 Gy to the tumor bed, again at a dosage of 2 Gy/day. Axillary node fields are not irradiated unless there is evidence that the patient is at high risk for axillary relapse—namely, multiple (generally more than four) positive lymph nodes, extranodal extension of tumor, or bulky axillary disease (i.e., palpable nodes several centimeters in diameter). Because the combination of surgical therapy and radiation therapy increases the risk of lymphedema of the arm, it is appropriate only when there is sufficient risk of axillary relapse to justify the increased complication rate. As a rule, supraclavicular node fields are irradiated only in patients with multiple positive axillary nodes, who are at increased risk for supraclavicular disease. The role of prophylactic irradiation of the internal mammary nodes remains controversial.

Postmastectomy radiation therapy involves irradiation of the chest wall after removal of the breast; it is mainly reserved for patients with T3 or T4 primary tumors or multiple positive lymph nodes. Such therapy is recommended particularly when there are multiple positive axillary lymph nodes: significant axillary disease predicts higher rates of chest wall recurrence after mastectomy. Two series have suggested that postmastectomy radiation therapy significantly improves survival in premenopausal women with any positive axillary nodes.

Irradiation of the breast or the chest wall is generally well tolerated: most women experience only minor side effects, such as transient skin erythema, mild skin desquamation, and mild fatigue. Because a small amount of lung volume is included in the irradiated fields, there is usually a clinically insignificant but measurable reduction in pulmonary function. In addition, because the heart receives some radiation when the left breast or the left chest wall is treated, there may be a slightly increased risk of future myocardial infarction. There is also a 1% to 2% chance that the radiation will induce a second malignancy (sarcoma, leukemia, or a second breast carcinoma). These radiation-induced malignancies appear after a long lag time, generally 7 to 15 years or longer.

Systemic Drug and Hormone Therapy  

Despite the success of surgical treatment and radiation therapy in achieving local control of breast cancer, distant metastases still develop in many patients. Various drugs and hormones have therefore been used to treat both measurable and occult metastatic disease. Now that many clinical trials have demonstrated a survival benefit, more and more women are receiving adjuvant cytotoxic chemotherapy. It became clear in early trials that multiple-agent (or combination) chemotherapy was superior to single-agent chemotherapy. It also became clear that chemotherapy and hormone therapy were limited in their ability to control large tumor masses, though on occasion, patients with large tumor masses showed dramatic partial responses or even complete responses to therapy.

With the goal of eradicating breast cancer metastases while they are still microscopic, systemic therapy is now administered in a so-called adjuvant setting—that is, when there is no evidence of distant metastases but there is sufficient suspicion that metastasis may have occurred. Until the late 1980s, adjuvant chemotherapy was given primarily to women who had axillary node metastases but no other evidence of disease. In node-positive premenopausal women, adjuvant chemotherapy appeared to be significantly more beneficial than adjuvant hormone therapy. In node-positive postmenopausal women, on the other hand, hormone therapy appeared to be as beneficial as chemotherapy and less toxic.

This approach to adjuvant systemic therapy changed in 1988, when the National Cancer Institute (NCI) issued a clinical alert stating that there was sufficient evidence of benefit to allow recommendation of adjuvant chemotherapy or hormone therapy for even node-negative breast cancer patients. By that time, a number of studies had shown that adjuvant chemotherapy could improve survival in node-negative breast cancer patients. A consensus conference of experts in the field suggested that such therapy be reserved for node-negative women with primary tumors larger than 1 cm in diameter. In 1992, a meta-analysis
that reviewed the treatment of 75,000 women in 133 randomized clinical trials of adjuvant therapy for breast cancer concluded that in node-negative premenopausal women, overall long-term survival was 20% to 30% higher for those who received chemotherapy than for those who did not. This benefit also appeared to extend to postmenopausal women between 50 and 60 years of age.

A number of prospective, randomized clinical trials have now shown that the use of trastuzumab with adjuvant chemotherapy leads to a marked improvement in disease-free and overall survival in patients with HER-2/neu–positive tumors. One study has found trastuzumab therapy to be associated with a 33% reduction in the risk of death. Trastuzumab has also been associated with a 0.5% to 4.1% 3-year cumulative risk of class III/IV congestive heart failure or cardiac death. In view of this risk, along with the known cardiotoxicity associated with anthracycline use, cardiac function should be monitored during trastuzumab therapy.

A 1998 overview of the use of adjuvant tamoxifen in randomized trials demonstrated that women with ER-positive tumors who were given tamoxifen for 5 years had a 47% reduction in tumor recurrence and a 26% reduction in mortality, compared with similar patients who were given placebo. In this analysis, the effects of tamoxifen on recurrence and survival were independent of age and menopausal status. Tamoxifen did not appear to improve survival, however, in women with ER-negative tumors. These results, together with data on the efficacy of tamoxifen for chemoprevention, have led to increased use of tamoxifen for premenopausal women and for women with small tumors.

Although tamoxifen is an excellent therapeutic agent and remains the standard therapy for hormone receptor–positive breast cancers in premenopausal women, aromatase inhibitors have proved to be superior for treating such cancers in postmenopausal women. These agents are pure antiestrogens: they function by preventing the peripheral conversion of fat and other substrates to estrogen. The first published study to demonstrate the superiority of an aromatase inhibitor to tamoxifen was the Arimidex (i.e., anastrozole), Tamoxifen, Alone or in Combination (ATAC) trial. This study showed that anastrozole, 1 mg daily, was superior to tamoxifen, 20 mg daily, and that there was no added benefit to the combination of the two drugs. These two medications have different side-effect profiles: tamoxifen is associated with an increased risk of thromboembolic events and endometrial cancer, whereas anastrozole is associated with bone loss and joint aches. After a median follow-up period of 68 months, anastrozole therapy was associated with significant prolongation of disease-free survival (575 events with anastrozole versus 651 with tamoxifen) and time to recurrence (402 recurrences versus 498), as well as significant reduction of distant metastases (324 distant metastases versus 375) and contralateral breast cancers (35 contralateral cancers versus 59); however, it yielded no significant improvement in overall survival. Anastrozole seems to be particularly effective for treatment of ER-positive, PR-negative tumors, which are more resistant to tamoxifen therapy. Other aromatase inhibitors have also been evaluated against tamoxifen. One such agent, letrozole, has been shown to be superior to tamoxifen as initial therapy and to be beneficial when taken for an additional 5 years after completion of a 5-year course of tamoxifen. Another such agent, exemestane, has been studied in a crossover fashion: 2 to 3 years of tamoxifen followed by 2 to 3 years of exemestane has been shown to be superior to 5 years of tamoxifen alone. Although it seems clear that in general, aromatase inhibitors are superior to tamoxifen, the data are currently insufficient to determine which of the various strategies for their use is the best. Further study is needed to determine the optimal sequence of therapy.

Now that it has been established that hormonal agents are highly effective in treating hormone receptor–positive tumors, the next challenge is how best to determine which early node-negative, hormone receptor–positive tumors might behave aggressively and thus might usefully be treated with adjuvant chemotherapy. The traditional predictive tools have led physicians to treat a substantial number of women in order to benefit very few. However, molecular diagnostic tests now exist that may facilitate decision making for patients with these tumors. The most widely used of these tests is Oncotype DX (Genomic Health, Inc., Redwood City, California), a 21-gene assay that addresses the biology of the tumor and generates a recurrence score. Patients with low recurrence scores tend to do well with hormonal therapy alone, whereas those with high recurrence scores tend to benefit from the addition of adjuvant chemotheraphy.

Locally Advanced Cancer

Patients with locally advanced breast cancer include those with primary tumors larger than 5 cm (particularly those with palpable axillary lymph nodes), those with fixed or matted axillary nodes, and those with inflammatory breast carcinoma. These patients are at high risk for systemic disease, as well as for local failure after standard local therapy. Current practice is to administer multimodality therapy, with chemotherapy as the first treatment modality. This so-called neoadjuvant chemotherapy often has the effect of downstaging local disease, in some cases making inoperable tumors amenable to surgical resection. Patients are treated with FNA, core-needle, or open incisional biopsy to obtain a tissue diagnosis, hormone receptor data, and HER-2/neu status; they then undergo careful restaging after systemic therapy to identify any distant metastases. If the tumor responds to chemotherapy, the patient may then undergo radiation therapy, surgery, or both. Most patients require all three modalities for optimum local and systemic control.

The optimal treatment of patients with stage IIIa breast cancer remains controversial. Some practitioners favor neoadjuvant chemotherapy, whereas others favor surgery followed by chemotherapy and radiation therapy. The choice of surgical procedure for women with locally advanced breast cancer is also controversial. Whereas many surgeons favor mastectomy for all tumors larger than 5 cm, others offer wide excision with axillary dissection to patients in whom excision to clean margins will leave a cosmetically acceptable breast.

Stage IV Cancer

Patients with distant metastases, whether at their initial presentation or after previous treatment for an earlier-stage breast cancer, are rarely cured. Before treatment begins, a tissue diagnosis consistent with breast cancer must be obtained from the primary lesion (at the initial presentation of the disease) or from a metastasis (if there is any doubt about the metastatic nature of the lesion or the source of the metastatic disease). Any tis-
sue samples obtained should be sent for ER and PR assays and determination of HER-2/neu status.

The usual first-line treatment for metastatic breast cancer is cytotoxic chemotherapy or hormone therapy. Radiation therapy may be used to relieve pain from bone metastases or to avert a pathologic fracture at a site of metastatic disease. There is also occasionally a role for so-called toilet mastectomy for patients who have metastatic disease and a locally advanced and ulcerated primary tumor if the condition of the primary tumor prevents the administration of needed chemotherapy. In fact, the current literature suggests that even in the presence of metastatic disease, surgical removal of the primary tumor improves survival.57-58

Treatment for stage IV breast cancer should be on protocol whenever possible. For patients who are ineligible for therapy on protocol, palliative chemotherapy or hormone therapy may be the best treatment option.

**BREAST CANCER IN PREGNANCY**

Breast cancer is the second most common malignancy associated with pregnancy (after cervical cancer), occurring during 1 of every 3,000 pregnancies.49 The diagnosis of breast cancer in pregnancy is often delayed because of the physiologic changes that pregnancy induces in the breast. To minimize diagnostic delays, all breast masses detected in pregnant women should be thoroughly evaluated. If mammography is truly indicated, it may be safely performed on a pregnant patient, provided that the fetus is appropriately shielded. Ultrasonography may also be quite helpful in evaluating breast masses in pregnant women.

Once the diagnosis is made, therapy depends on the stage of the pregnancy. Termination of pregnancy usually is not necessary for treatment of the cancer. Because exposure to radiation is contraindicated at all stages of pregnancy, mastectomy is generally necessary for all patients except those whose cancers are diagnosed at a late stage, for whom radiation therapy can reasonably be delayed until after delivery. For this reason, mastectomy is the preferred surgical therapy in most instances. Breast conservation may be performed if the cancer is diagnosed in the third trimester. As far as axillary staging is concerned, there have been no reported consequences to either the mother or the fetus from injections of technetium-99m–labeled sulfur colloid, and it is generally considered fairly safe to use radioisotopes in the performance of SLNB. The safety of isosulfan blue dye in pregnancy is less clear, and vital blue dyes usually are best avoided. With respect to chemotherapy, administration of cytotoxic agents should be avoided in the first trimester but is considered to be much less risky—and therefore acceptable—in the second and third trimesters.

**BREAST CANCER IN MEN**

Fewer than 1% of all breast carcinomas occur in men. Presdisposing risk factors include conditions associated with increased estrogen levels (e.g., cirrhosis and Klinefelter syndrome) and radiation therapy.50 In addition, an increased incidence of male breast cancer has been reported in families in which the BRCA2 mutation has been identified. As with breast cancer in women, the most common tumor type is infiltrating ductal cancer. Because breast cancer tends to be detected at a later stage in men than in women, there is a misconception that male breast cancer has a worse prognosis. Stage for stage, however, the prognosis for men with breast cancer is similar to that for women with breast cancer. To prevent late detection, men with a breast mass must be evaluated with the same degree of suspicion as women with a breast mass.

Surgical treatment includes mastectomy. In the absence of clinically palpable nodes, SLNB is appropriate for staging the axilla. A large majority of male breast cancers are ER positive, and decisions regarding adjuvant systemic treatment should be made on the same basis as for breast cancer in women.

**FOLLOW-UP AFTER TREATMENT**

Patients who have been treated for breast cancer remain at risk for both the recurrence of the original tumor and the development of a new primary breast cancer. The rate of recurrence of breast cancer is nearly linear over the first 10 years after treatment. Recurrence becomes less likely after the first decade, but it continues at a significant rate through the second decade and beyond. In patients who have undergone limited surgery and radiation therapy, radiation-induced breast and chest wall malignancies begin to appear 7 or more years after treatment and continue to appear for at least 20 years after treatment.

Unfortunately, there is little in the way of evidence-based guidance to help the clinician determine the optimal posttreatment surveillance strategy for breast cancer patients. As a result, practice patterns vary considerably with respect to the use of follow-up tests in this population. Exhaustive posttreatment testing does not seem warranted in early-stage breast cancer patients. There is no evidence to support the use of routine bone scans, computed tomography, PET brain imaging, or serum tumor markers in asymptomatic patients after treatment for early-stage disease. The use of such intensive surveillance is based on the presumption that detecting disease recurrence at its earliest stage would offer the best chance of cure, improved survival, or, at least, improved quality of life. Given that the majority of recurrences are detected by patients themselves, educating patients about the symptoms of recurrent disease is likely to be a more effective strategy.

Follow-up of early-stage breast cancer patients should include a thorough history and physical examination and mammography. For patients treated with breast conservation, annual mammography is appropriate, beginning after any acute radiation reaction has resolved (generally 6 to 9 months after completion of radiation therapy). For patients treated with mastectomy, mammography should be continued on an annual basis for the contralateral breast. Physical examination and review of symptoms are generally performed at 3- to 6-month intervals for the first 5 years after completion of therapy, though these intervals have not yet been tested in a prospective fashion.

Although there has been little debate about the value of early detection of a local recurrence within the treated breast or of a new primary tumor in either breast, there has been a great deal of debate about the value of early detection of metastatic disease. Two prospective, randomized trials addressed this issue. In one, a group of breast cancer patients was intensively followed with blood tests every 3 months and with chest x-rays, bone scans, and liver ultrasonography annually.52 There was no difference in survival or quality of life between this group and the control group, and metastatic disease was diagnosed, on average, less than 1 month earlier in the intensively followed group than in the control group. In the second study, a group of breast cancer patients received chest x-rays and bone scans every 6 months for 5 years.52 Pulmonary and bone metastases were detected significantly earlier in this group than in the control group, but there was no improvement in survival. This study demonstrated that early detection of metastatic disease could be achieved with short-interval screening, but given current therapeutic options, early detection had no beneficial effect on survival. Both studies concluded that at present, there is no role for routine imaging studies in the follow-up of breast cancer patients and that imaging studies should be ordered only as prompted by clinical findings.
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