Breast cancer is a major cause of morbidity and mortality across the world. In the United States, each year about 180,000 new cases are diagnosed with more than 40,000 deaths annually (Jemal et al., 2007). It is a highly heterogeneous disease, both pathologically and clinically. Although age is the single most common risk factor for the development of breast cancer in women (see Fig. 10.13), several other important risk factors have also been identified, including a germline mutation (BRCA1 and BRCA2) (Table 10.1), positive family history, prior history of breast cancer, and history of prolonged, uninterrupted menses (early menarche and late first full-term pregnancy) (Table 10.2).

Much progress has been made in the diagnosis and treatment of primary and metastatic breast cancer. The widespread use of routine mammography has led to an increased incidence in the detection of early primary lesions, a factor that has contributed to a significant decrease in mortality (see Figs. 10.38 to 10.41, 10.44). Magnetic resonance imaging (MRI) of the breast may be useful in screening women with a higher lifetime risk of breast cancer, such as those women with a BRCA1/2 mutation or with a family history strongly suggestive of a hereditary breast/ovarian

<table>
<thead>
<tr>
<th>Table 10.1</th>
<th>Estimated Lifetime Incidence of Cancer for BRCA1/2 Mutation Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Cancer</td>
<td>BRCA1 Carrier</td>
</tr>
<tr>
<td>Breast</td>
<td>40–85</td>
</tr>
<tr>
<td>Ovarian</td>
<td>25–65</td>
</tr>
<tr>
<td>Male breast</td>
<td>5–10</td>
</tr>
<tr>
<td>Prostate</td>
<td>Elevated*</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

*Prostate cancer risk is probably elevated, but absolute risk is not known. Adapted from Table 19.1 in Harris et al., 2004.

<table>
<thead>
<tr>
<th>Table 10.2</th>
<th>Selected Breast Cancer Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
<td>Referent</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Age at menarche</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>None</td>
</tr>
<tr>
<td>Age at first birth</td>
<td>&lt;20–22</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>None</td>
</tr>
<tr>
<td>Parity</td>
<td>0</td>
</tr>
</tbody>
</table>

Age at menopause

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Referent</th>
<th>Comparison</th>
<th>Approximate Relative Risk</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical oophorectomy</td>
<td>50+</td>
<td>&lt;40</td>
<td>0.6</td>
<td>Brinton et al. (1988)</td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>None</td>
<td>Current use for 5 years</td>
<td>1.2–1.3</td>
<td>Rossouw et al. (2002)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>&lt;21</td>
<td>&gt;28–30</td>
<td>0.5–0.7</td>
<td>Ursin et al. (1995); van den Brandt et al. (2000)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>None</td>
<td>Moderate</td>
<td>1.2–1.3</td>
<td>Thune et al. (1997); McTiernan et al. (2003)</td>
</tr>
<tr>
<td>Serum estradiol (postmenopausal)</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>2</td>
<td>Key et al. (2002)</td>
</tr>
<tr>
<td>Mammographic breast density</td>
<td>&lt;25% density</td>
<td>&gt;75% density</td>
<td>4–6</td>
<td>Boyd et al. (1998)</td>
</tr>
<tr>
<td>Bone density</td>
<td>Lowest quartile</td>
<td>Highest quartile</td>
<td>2.0–3.5</td>
<td>Cauley et al. (1996); Zhang et al. (1997)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>None</td>
<td>3+ drinks per day</td>
<td>1.3–1.4</td>
<td>Smith-Warner et al. (1998); Hamajima et al. (2002)</td>
</tr>
<tr>
<td>Benign breast disease (atypical hyperplasia)</td>
<td>No</td>
<td>Yes</td>
<td>2–6</td>
<td>Dupont and Page (1985); Marshall et al. (1997)</td>
</tr>
<tr>
<td>Family history of breast cancer in first-degree relative</td>
<td>None</td>
<td>1+</td>
<td>2–4</td>
<td>Collaborative Group (2001)</td>
</tr>
</tbody>
</table>
syndrome (Saslow et al., 2007) (see Fig. 10.7). Moreover, less aggressive, conservative local therapy has been shown to be as effective as mastectomy in prolonging survival, while avoiding the cosmetic disfigurement associated with more extensive surgery. Sentinel node biopsy (see Fig. 10.78) is now routinely being offered to appropriate patients, with a significant decrease in the morbidity associated with the traditional axillary node dissection. Adjuvant systemic therapy, such as chemotherapy and/or hormonal therapy, has also contributed to the prolonged survival of patients with breast cancer (EBCTCG, 2005). The identification of molecular targets such as the overexpression of HER2/neu has allowed biologic therapies directed against the HER2/neu pathway to be considered part of standard treatment in both the adjuvant and metastatic setting for tumors that overexpress HER2/neu (Piccart-Gebhart et al., 2005; Romond et al., 2005).

**Incidence**

Breast cancer incidence has remained level during the last decade. Breast cancer deaths are decreasing, primarily for white women and younger women. Although white women develop breast cancer more frequently, black women are more likely to die of the disease (Jemal et al., 2007; Smigal et al., 2006) (Fig. 10.8A, B).

**Screening**

Routine mammographic screening allows better detection of primary breast cancers than physical examination. Mammographic screening has been shown to decrease mortality rates in women 50–69 years of age. A 26% decrease in the relative risk of breast cancer was noted with screening mammography in this group. The enthusiasm for screening has led to the detection of small primary lesions that pose difficult diagnostic dilemmas when breast biopsies reveal premalignant histopathologic findings. The diagnosis of in situ carcinomas appears to be increasing in frequency. Noninvasive breast cancer includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS is described as the proliferation of malignant epithelial cells confined to the mammary ducts without evidence of invasion through the basement membrane (see Figs. 10.14, 10.16 to 10.20, and 10.22) and is considered a precursor lesion. DCIS (also called intraductal carcinoma) is more likely to be localized to a region within one breast. Variants include papillary carcinoma in situ (see Fig. 10.21) which may mimic benign atypical papillomatosis, and comedo carcinoma, which consists of a solid growth of neoplastic cells within the ducts, associated with centrally located necrotic debris (Burstein et al., 2004).

In contrast, LCIS (see Figs. 10.23, 10.24) tends to be diffusely distributed throughout both breasts. LCIS is considered a risk factor for breast cancer and is not a precursor lesion (Page et al., 1991; Chuba et al., 2005). DCIS is more common than LCIS, representing about 20% of breast cancers diagnosed in the United States (Ernster et al., 2002). Although the prognosis for patients with both types of in situ lesions is excellent, invasive lesions will develop in a certain fraction of patients with in situ carcinomas. Surgery, as either mastectomy or breast-conserving surgery plus adjuvant radiation, has been the treatment of choice for DCIS (Fisher et al., 1993; Julien et al., 2000). Selective estrogen receptor modulators, such as tamoxifen, may further decrease recurrence risk (Fisher et al., 1999). Management options for LCIS include careful observation or bilateral prophylactic simple mastectomy or the use of tamoxifen.

**Histology**

**IN SITU BREAST CANCERS AND NONINVASIVE BREAST CANCER**

The diagnosis of in situ carcinomas appears to be increasing in frequency. Noninvasive breast cancer includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS is described as the proliferation of malignant epithelial cells confined to the mammary ducts without evidence of invasion through the basement membrane (see Figs. 10.14, 10.16 to 10.20, and 10.22) and is considered a precursor lesion. DCIS (also called intraductal carcinoma) is more likely to be localized to a region within one breast. Variants include papillary carcinoma in situ (see Fig. 10.21) which may mimic benign atypical papillomatosis, and comedo carcinoma, which consists of a solid growth of neoplastic cells within the ducts, associated with centrally located necrotic debris (Burstein et al., 2004).

Over half of all women will develop benign breast lesions. These include macro- and microcysts, adenosis, apocrine changes, intraductal papillomas, fibrosis, fibroadenomas, and epithelial hyperplasias (see Figs. 10.2 to 10.6 and 10.9 to 10.12). Only the latter, however, particularly those showing atypia, are believed to be precursors to the development of malignancy (Dupont et al., 1993; Marshall et al., 1997). Benign lesions may present with pain, tenderness, and nipple discharge, as well as masses and dimpling of the skin. Mammographic changes, such as densities and microcalcifications, may also be noted in benign lesions and at times, may mimic malignancies.

**INVASIVE BREAST CANCERS**

Over 75% of all infiltrating breast cancers originate in the ductal system (see Figs. 10.1, 10.27 to 10.29; Table 10.3). Several histologic variants of ductal carcinoma have been described. Pure examples of these variants constitute only a small percentage of the total number of cases, but certain features of each may be seen within the main portions of tumors that show the more common presentation designated invasive (or infiltrating) ductal carcinoma. Medullary carcinoma (see Fig. 10.32) is distinguished by poorly differentiated nuclei and infiltration by lymphocytes and plasma cells, whereas tubular carcinomas (see Fig. 10.31) are highly differentiated tumors that are marked, as their name suggests, by tubule formation. In mucinous (or colloid) carcinomas (see Fig. 10.33), nests of neoplastic epithelial

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**Table 10.3**

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal</td>
<td>75.8</td>
</tr>
<tr>
<td>Lobular</td>
<td>8.3</td>
</tr>
<tr>
<td>Ducto lobular</td>
<td>7.1</td>
</tr>
<tr>
<td>Mucinous (colloid)</td>
<td>2.4</td>
</tr>
<tr>
<td>Comedocarcinoma</td>
<td>1.6</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>1.6</td>
</tr>
<tr>
<td>Tubular</td>
<td>1.5</td>
</tr>
<tr>
<td>Medullary</td>
<td>1.2</td>
</tr>
<tr>
<td>Papillary</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Note: Other miscellaneous tumors (e.g., metaplastic, adenocystic, micropapillary, apocrine, Paget’s) were not included in the above list. They compose <5% of invasive breast cancers.

From Lie et al. (2005).
cells are surrounded by a mucinous matrix. A few invasive ductal carcinomas exhibit papillary features; hence their designation as papillary carcinomas. Although the above variants may carry a more favorable prognosis than routine infiltrating ductal carcinomas, they are treated similarly, based on stage of disease.

About 5% to 10% of infiltrating cancers arise from the lobules (see Fig. 10.30). Histologically, neoplastic cells of these tumors manifest a distinctive “single file” pattern. The prognosis and treatment of invasive lobular carcinoma are nearly identical to those of the invasive ductal type. However, lobular carcinomas can occasionally metastasize to the serosal surfaces of the abdominal organs, mimicking ovarian cancer (see Fig. 10.8C). Other unusual malignancies can develop in the breast, including apocrine, metaplastic, adenoid cystic, and squamous cell carcinomas. The cell of origin of the latter three has been difficult to determine. Fibroepithelial malignancies, such as cystosarcoma phyllodes, are occasionally found in the breast, arising from the mesenchymal stroma (see Fig. 10.34) (Harris et al., 2004).

**Diagnosis and Staging of Breast Cancer**

Previously, open surgical biopsies were performed for diagnosis of breast cancer (see Fig. 10.68). Now, core needle biopsies are generally performed initially and usually yield sufficient tissue for histologic and immunohistochemical examinations. Needle biopsy can be done with ultrasound or stereotactic guidance (see Fig. 10.8D, E).

After a cancer diagnosis has been established, staging evaluation first begins with a detailed history and physical examination. Particular attention is given to the size, consistency, and fixation of the breast mass, skin changes such as erythema, edema, dimpling, and satellite nodules, as well as nipple changes such as retraction, discharge, and thickening. The status of axillary and infra- and supraclavicular lymph nodes is also evaluated. Chest and abdominal computed tomography (CT) scans and bone scans are performed in patients with node-positive disease and those with localizing symptoms. Head CTs are not routinely done unless patients are experiencing symptoms such as unusual headaches, nausea, cranial nerve deficits, and/or gait disturbances. Determination of biologic tumor markers (e.g., carcinoembryonic antigen [CEA], CA27, CA29) may be useful in patients with metastatic cancer. More recently, positron emission tomography (PET)-CTs have been used for staging and diagnosing recurrences, because they may have higher specificity for metastatic disease than standard CT (Radan et al., 2006) (Fig. 10.8F).

Historically, staging systems were based on the findings of the clinical examination, in particular on the size of the primary lesion and the extent of metastases to regional lymph nodes (see Figs. 10.36 through 10.38). Currently for breast cancer, pathologic findings have become the standard for determination of staging. In particular, lymph nodes may harbor microscopic metastases that would not be clinically or radiographically apparent (see Fig. 10.51). Stage I breast cancers consist of small lesions (<2 cm) with no palpable adenopathy; these account for approximately 60% or more of all newly diagnosed breast cancers. Stage II or III breast cancer has either a larger primary tumor (>2 cm) and/or axillary lymph node involvement. For clinical staging, it is important to determine whether the patient has palpable cervical, supraclavicular, or axillary lymphadenopathy, although these will have to be confirmed by biopsy. The diagnosis of inflammatory breast cancer can be made on pathologic and clinical grounds (e.g., skin edema, erythema, or thickening; see Figs. 10.43 through 10.48). Patients are considered to have stage IV disease if they have any evidence of distant metastases (see Fig. 10.53). Ipsilateral supraclavicular lymphadenopathy is now considered stage IIIC (AJCC, 2002; Harris et al., 2004).

Although even within a stage breast cancer can be heterogeneous, the presence of metastases to axillary lymph nodes (designated pathologic stage II or III) is the single most important prognostic factor in patients with breast cancer. Over 95% of patients with stage I disease are alive 10 years after diagnosis. The overall survival rates at 5 years for patients with stage II and stage III breast cancer are 80% to 90% and 50% to 70%, respectively. Patients with metastatic disease (stage IV) are rarely, if ever, cured, but approximately 20% are still alive 5 years after metastases are detected (see Fig. 10.37).

### Primary Treatment

In the late nineteenth century, the technique of mastectomy was pioneered by Halsted and found to improve local control of breast cancer. For the next 50–75 years the concept that breast cancer spread in an orderly fashion from the primary lesion to regional lymph nodes and then to distant organs dominated the treatment of early disease (see Figs. 10.15, 10.16). During this time radical mastectomy (the complete removal of the breast, pectoral muscles, and axillary contents) was the treatment of choice. Subsequent studies have demonstrated that patients treated with less aggressive (modified radical) mastectomies have the same survival as those treated with radical mastectomies. In the last 20 years breast-conserving therapy, in which the initial mass is removed by “lumpectomy” or “quadrantectomy,” followed by primary irradiation to the remainder of the breast, has been shown to produce survival rates similar to those seen with treatment by mastectomy. In most cases less aggressive, breast-conserving local therapy provides excellent cosmetic results (see Figs. 10.69, 10.70).

There are also new advances in exploring the axilla for the determination of lymph node involvement. A sentinel axillary lymph node is the first area to receive lymph flow and is usually the first to harbor a metastasis from the breast cancer. In selected patients a sentinel node biopsy serves as a means of avoiding a complete axillary dissection and is the preferred manner to assess disease in the axilla. To localize the sentinel node, surgeons inject one or two markers, blue dye or technetium sulfur colloid—$^{99}$Tc, around the tumor or biopsy cavity. The markers are taken up into the lymphatic channels surrounding the tumor site and travel to the nodal basin. In some situations lymphoscintigraphy is performed after the injection to map out the lymphatic drainage pattern. A positive sentinel node requires a full axillary dissection (see Fig. 10.78). If the sentinel node biopsy is negative a full axillary dissection can be spared, eliminating the known potential complications of a dissection such as lymphedema (see Fig. 10.77) (Veronesi et al., 2003).

The completion of breast conservation therapy involves radiation therapy. The whole breast is treated using a pair of tangentially directed fields. The fields are designed to skin along the chest wall and thus irradiate the smallest amount of underlying lung.
At the conclusion of the whole-breast treatment, a boost dose is often given to the tumor bed. Complications of radiation therapy include radiation pneumonitis (see Fig. 10.81). In certain selected patients partial breast irradiation is also being performed, although little long-term data exist to accurately evaluate its equivalence to standard whole-breast irradiation (see Fig. 10.8G).

Such conservative therapy, however, is not appropriate for all patients. Contraindications to breast-conserving surgery include multicentric disease, diffuse malignant microcalcifications, and previous breast radiation therapy. For those who require or prefer mastectomies, remarkable advances have been made in recent years in reconstructive surgery (see Figs. 10.71 through 10.75). Some women will still require radiation therapy after mastectomy, including those with multiple involved lymph nodes or larger primary tumors.

Advances in local therapy have been complemented by the recent demonstration that adjuvant systemic therapy significantly prolongs survival compared with observation alone for certain subgroups of patients. Prognostic factors for stages I–III breast cancer include lymph node status, tumor size, estrogen/progesterone receptor, tumor kinetics, and overexpression/over-amplification of HER2/neu (Table 10.4).

**Metastatic Breast Cancer/Locally Recurrent Disease**

Locally recurrent disease is often manifested by subcutaneous nodules or a nodular cutaneous rash along the mastectomy site. Occasionally the subcutaneous nodules become confluent and extend across the chest wall. The confluence is called an “en cuirasse” carcinoma (see Figs. 10.49, 10.50).

Although median survival for metastatic breast cancer is 2–3 years, patients with metastatic breast cancer demonstrate considerable heterogeneity in the clinical course of their disease. Some patients have a rapidly progressing tumor that metastasizes to multiple organs, whereas others have more indolent disease with a small percentage of patients considered “long-term” survivors (>10 years). Survival for patients with metastatic disease varies according to certain prognostic factors: a long, disease-free interval after primary therapy is a more favorable prognostic factor than a short interval; nonvisceral sites of metastases, free interval after primary therapy is a more favorable prognosis, compared to symptoms referable to the organ involved (e.g., bone pain, shortness of breath, anorexia, or motor and/or neurologic deficits). Interestingly, tumors that overexpress HER2/neu appear to have a higher rate of brain metastases than HER2/neu-negative cancers (Bendell et al., 2003; Clayton et al., 2004). Although local-regional recurrence can sometimes represent a harbinger for metastatic (stage IV) disease, aggressive multimodality therapy can be associated with long-term disease control. Approximately 5% of newly diagnosed cases present with disseminated metastatic disease.

Until recently, hormonal therapy and chemotherapy have formed the foundation of treatment. Different types of hormonal agents, including SERMs (serotonin receptor modulators), SERDs (serotonin receptor downregulators), aromatase inhibitors, and luteinizing hormone–releasing hormone agonists, have contributed to the management of women with metastatic hormone-responsive disease. Complications of therapy can lead to myelosuppression, nausea, vomiting, alopecia, neurotoxicity, and integumentary toxicity (see Fig. 10.80). In addition to standard cytotoxic and hormonal therapies, targeted biologic therapies are increasingly used. The most widely used target the HER2/neu pathway and include trastuzumab, a humanized monoclonal antibody to the HER2/neu protein, and lapatinib, an oral dual tyrosine kinase inhibitor of the HER2/neu and epidermal growth factor receptor (EGFR) pathways. HER2/neu is overexpressed in approximately 25% to 30% of breast cancers (see Fig. 10.81H). Several methods of detection of HER2/neu are used. Immunoperoxidase studies use antibodies directed at HER2/neu protein. A more accurate but labor-intensive method looking at the amplification of the gene is fluorescent in situ hybridization (FISH) (see Fig. 10.79). Trastuzumab has been incorporated into the standard treatment in both the adjuvant and metastatic settings for appropriate patients. In addition, agents that target the vascular endothelial growth factor (VEGF) and/or EGFR pathway also appear to have activity in metastatic breast cancer.

Additionally, selective use of surgery or radiation therapy and use of bisphosphonates can provide significant palliation to patients with metastases. Bisphosphonates are routinely used in women with bone metastases to decrease the risk of skeletal complications (Theriault et al., 1999). Monitoring of tumor markers (CEA or CA15-3 or CA27-29) is often helpful in monitoring disease course (see Fig. 10.67). Tumor markers alone, however, should not be the sole determinant of treatment response, because they can transiently increase soon after starting treatment (“flare response”) or may be elevated by non-neoplastic causes. In addition, some women with metastatic breast cancer have normal tumor markers.

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**Table 10.4**

<table>
<thead>
<tr>
<th>Adverse Prognostic Factors in Breast Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node status</td>
</tr>
<tr>
<td>Negative &lt; few positive &lt; many positive</td>
</tr>
<tr>
<td>Larger tumor size</td>
</tr>
<tr>
<td>Clinical features: fixation; ulceration; inflammation</td>
</tr>
<tr>
<td>High histologic grade</td>
</tr>
<tr>
<td>High nuclear grade</td>
</tr>
<tr>
<td>Estrogen-receptor (ER) and progesterone-receptor (PR) content negative</td>
</tr>
<tr>
<td>Tumor kinetics</td>
</tr>
<tr>
<td>Thymidine-labeling index; high S-phase fraction</td>
</tr>
<tr>
<td>DNA aneuploidy</td>
</tr>
<tr>
<td>HER2/neu overexpression/overamplification</td>
</tr>
<tr>
<td>Basal phenotype (“triple negative” or ER/PR/HER2/neu-negative)</td>
</tr>
</tbody>
</table>

*Adapted from Hayes (1993a) and McGuire and Lark (1992).*
FIGURE 10.1 BREAST ANATOMY. Within the breast the epithelial elements are organized into lobular units consisting of acini that feed into ductules. The latter in turn coalesce into larger ducts that form a reservoir, or lactiferous sinus, proximal to the nipple. These epithelial structures, supported by adipose and fibrous tissue, give rise to more than 95% of breast malignancies.

FIGURE 10.2 FIBROADENOMA. The tumor from which this histologic section was taken was a well-circumscribed, discoid mass, clearly demarcated from the surrounding breast tissue. High magnification reveals stroma compressing ducts so that they form slitlike curvilinear spaces. Note the low cellularity of the stroma, an important benign feature.

FIGURE 10.3 LACTATING ADENOMA. This well-circumscribed lesion has closely packed acini with prominent epithelial cells marked by large nuclei and abundant, pink, vacuolated cytoplasm. (Courtesy of Dr N. Weidner, Brigham and Women's Hospital, Boston, MA.)
FIGURE 10.4  SCLEROSING ADENOSIS. (A) Low-power microscopic section shows distortion of the lobular architecture; there is an increase in acini (terminal ductules), appearing in a whorled, expansile, and vaguely defined pattern. The low-power view is very helpful in distinguishing this benign proliferation from malignancy. (B) Higher magnification shows that the acini are composed of a normal two-cell population.

FIGURE 10.5  PAPILLOMA. Low-magnification view shows a large duct filled with a papillary proliferation. At higher power (inset) a papillary branch can be seen with a normal two-cell population covering a fibrovascular stalk. In this benign tumor the lining epithelial cells can show apocrine changes.

FIGURE 10.6  FIBROCYSTIC CHANGES. These benign changes are the most common findings in breast biopsies. They are characterized by dense fibrosis intermixed with cystic areas.
FIGURE 10.7 (A) Bilateral mammograms on a 45-year-old patient with enlarged right axillary nodes (black arrow) but no mammographic abnormality within either breast. (B) Sagittal MR image of the right breast with fat saturation before administration of gadolinium. A rounded density represents an axillary node (white arrow). (C) Sagittal MRI image at the same location as B after administration of gadolinium. Enhancement of the node is evident (white arrow). (D) Sagittal MRI image of the right breast at a level slightly medial to B and C. A patch of stromal density is evident deep in the breast before contrast administration (white arrow). Other retroareolar stromal densities with similar appearance are also present. (E) Sagittal MRI image of the right breast in the same location as D, after administration of gadolinium. The deep stroma is enhancing (white arrow) consistent with tumor, while the other stromal densities have not changed, consistent with normal breast tissue.
Receptor-specific ligands HER1, HER2, HER3, or HER4

Tyrosine kinase domains HER1 (EGFR), HER2, HER4

Cell proliferation

Cell survival

Cell mobility and invasiveness

Transcription

FIGURE 10.8 See legend on opposite page.
When lobular breast cancer metastasizes it can often infiltrate serosal surfaces mimicking ovarian cancer. This patient presented with abdominal bloating, tightness, and narrowing in her stool caliber 9 years after the diagnosis of a stage I breast cancer. Note the diffuse thickening of the rectal and colonic wall, peritoneal carcinomatosis, and ascites. A colonoscopy was performed, and biopsy confirmed diffuse involvement with metastatic adenocarcinoma consistent with a breast primary. On restaging, she was also noted to have multiple osseous metastases. (Image courtesy of Drs. Pamela Dipiro and Wendy Chen, Dana Farber Cancer Institute, Boston, MA.) (D) In an ultrasound-guided needle biopsy, the ultrasound probe is used to localize the lesion that was identified either on physical examination or on mammogram. A biopsy needle is passed through the lesion several times to obtain tissue. Compared to a stereotactic biopsy, an ultrasound-guided biopsy is faster and better tolerated by most patients. However, not all lesions may be amenable to an ultrasound-guided biopsy. (Image courtesy of Robyn L. Birdwell, MD, Brigham and Women’s Hospital, Boston, MA, and Diagnostic Imaging Breast, Amirsys, Inc., Salt Lake City, UT, 2006.) (E) The premise behind stereotactic needle biopsy is that a lesion can be localized in three dimensions by evaluating its changes in position in a series of angled radiographic views. First, a radiograph localizes the suspicious area, then two additional views, angled 15 degrees to either side of the lesion, are obtained. A computer calculates how much the lesion’s position appears to have changed on each of the angled views and uses these data to estimate the lesion’s location within three-dimensional space. With the advent of digital mammography these images are commonly acquired digitally. (Image courtesy of Robyn L. Birdwell, MD, Brigham and Women’s Hospital, Boston, MA, and Diagnostic Imaging Breast, Amirsys, Inc., Salt Lake City, UT, 2006.) (F) Positron emission tomography (PET) involves injection of a substance labeled with a positron-emitting isotope (commonly, fluorine-18 bound to D-glucose, called FDG for 2-[18F]fluoro-2-deoxy-D-glucose)). Metabolically active cells, especially malignant ones, preferentially take up glucose, and therefore FDG, as compared with non-neoplastic tissue. Sensitivity of PET can vary considerably by tumor type and size. False-positive results can occur in areas of inflammation or infection. Many machines now acquire CT images in tandem with PET images, which can then be fused together to provide anatomic correlation by CT with metabolic activity measurements by PET. This patient presented with palpable axillary adenopathy and a large breast mass with associated erythema, skin edema, and nipple retraction. Note the extremely intense areas of uptake within the right breast and axilla corresponding to the patient’s known locally advanced breast cancer. Also note the intense uptake in the right supraclavicular, paratracheal, prevascular, paracarinal, and hilar lymph nodes suspicious for metastatic disease. Uptake in the kidney, bladder, and ureters is physiologic and due to FDG excretion. Uptake in the right adnexa and jaw is most likely physiologic and benign. (G) Panels 1 and 2: Accelerated partial breast irradiation (APBI) encompasses techniques including intracavitary and interstitial brachytherapy as well as 3D-conformal, intensity-modulated, and intraoperative external-beam radiation therapy. One of the more commonly used brachytherapy methods in the United States, the MammoSite Brachytherapy System (Hologic, Massachusetts) involves insertion of a catheter with a balloon tip into the lumpectomy cavity at the time of surgery or shortly thereafter (panel 1). The balloon is filled with saline and a high-dose-rate radioactive source is introduced twice per day for 5 days by computed axial tomography scan–based treatment planning, permitting a highly conformal dose to be delivered to the first centimeter of remaining breast tissue with optimal sparing of the remaining tissue and other regional organs (panel 2). The balloon catheter is removed upon completion. APBI is an option only for selected patients, mainly older women with smaller, node-negative “low-risk” tumors and with negative margins. (Courtesy of Phillip M. Devlin, MD, Dana Farber/B Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA.) (H) The HER family of receptors (human epidermal growth factor receptor, also called ErbB) is a group of transmembrane tyrosine kinase receptors that regulate cell growth, survival, and differentiation, via a variety of pathways, including RAS (rat sarcoma), RAF (receptor activation factor), MAPK (mitogen-activated protein kinase), and MEK (mitogen extracellular signal kinase). The tyrosine kinase domains are activated by dimerization. Current therapeutics involve tyrosine kinase inhibitors (e.g., lapatinib) and antibodies directed against the HER2 protein and VEGF (vascular endothelial growth factor) (e.g., trastuzumab and bevacizumab).
FIGURE 10.11  EPITHELIAL HYPERPLASIA (FLORID). Involved spaces show marked distention by hyperplastic cells that occupy the majority of the lumen. Collapsed slitlike spaces are present, frequently at the periphery of the structure. These slits are surrounded by serpentine passages composed of “flowing” cells, which often lack clear cell borders. Moderate and florid hyperplasias imply a slightly higher risk of subsequent invasive carcinoma than mild or no hyperplasia.

FIGURE 10.12  EPITHELIAL HYPERPLASIA (ATYPICAL). (A) Atypical cases show a nonuniform population of cells from normochromatic nuclei surrounding spaces that are not quite smooth-lined. It is these features that distinguish atypical epithelial (ductal) hyperplasia from ductal carcinoma in situ, in which smooth, geometric spaces are surrounded by a uniform cell population with hyperchromatic nuclei. (B) High magnification shows that these proliferating, relatively nonuniform cells lack the necessary degree of cell-to-cell rigidity. Atypical hyperplasia carries a relatively higher risk of subsequent development of invasive carcinoma than other types. This risk is further elevated in women with a family history of breast cancer in a first-degree relative.

FIGURE 10.13  Age-specific incidence of breast cancer in the United States.
This theory suggests that breast cancer becomes metastatic very early in its course, once invasion through the basement membrane of the duct or lobule has occurred. It maintains that local therapy will have few if any long-term effects on survival, because the disease is already systemic at the time of diagnosis.

**FIGURE 10.16** systemic theory of breast cancer spread. This theory suggests that breast cancer becomes metastatic very early in its course, once invasion through the basement membrane of the duct or lobule has occurred. It maintains that local therapy will have few if any long-term effects on survival, because the disease is already systemic at the time of diagnosis.
FIGURE 10.17 INTRADUCTAL CARCINOMA (CRIBRIFORM TYPE). (A) Low- and (B) high-power photomicrographs demonstrate a cribriform pattern composed of a rather uniform tumor cell population with distinct cytoplasmic borders; the cells are rigidly arranged around crisp, circular holes. With this pattern the risk for the subsequent development of invasive cancer increases 10- to 11-fold. (Courtesy of Dr N. Weidner, Brigham and Women’s Hospital, Boston, MA.)

FIGURE 10.18 INTRADUCTAL CARCINOMA (COMEDO TYPE). (A) Low- and medium-power (inset) microscopic sections show expanded ducts with central necrosis. (B) At high magnification, cellular pleomorphism is also evident. This feature is seen to a greater extent and more commonly in the comedo type of ductal carcinoma in situ. Occult invasive elements may also be more common in the comedo than non-comedo types (see Figs. 10.18 to 10.20).

FIGURE 10.19 INTRADUCTAL CARCINOMA (“CLINGING” TYPE). Low- (inset) and high-power microscopic sections show tumor cells “clinging” to the periphery of a duct. The clusters of basophilic malignant cells show a high nucleus-to-cytoplasm ratio. Note the bridgelike structure formed by these cells on the high-power view.

FIGURE 10.20 INTRADUCTAL CARCINOMA (MICROPAPILLARY TYPE). (A) Low magnification reveals expanded ducts with fronds of tumor characteristically extending toward the center of the lumina. (B) At high magnification the bulbous fronds typically appear narrow at the base and expanded at the tip. (A, Courtesy of Dr N. Weidner, Brigham and Women’s Hospital, Boston, MA.)
FIGURE 10.21 PAPILLARY CARCINOMA IN SITU. The architectural features of this in situ breast cancer are similar to those of a papilloma. The normal two-cell-layer epithelium covering the fibrovascular fronds is replaced by a uniform proliferation of cells with hyperchromatic nuclei.

FIGURE 10.22 INTRADUCTAL CARCINOMA. (A) Microscopic section shows a normal lobular unit on the left and “cancerization of the lobules” on the right, where a ductal carcinoma has extended into the lobules. (B) High magnification demonstrates “cancerization of the lobules” in the upper portion of the field, whereas the lower portion reveals a duct that has been expanded by an intraductal carcinoma with foci of necrosis. “Cancerization of the lobules” carries no clinical significance except that it may mimic lobular carcinoma in situ. However, pleomorphism, tubule formation, and necrosis, as seen here, are not encountered in lobular carcinoma.

FIGURE 10.23 LOBULAR CARCINOMA IN SITU. Low-power photomicrographs show (A) the normal architecture of a lobular unit and (B) a distended lobular unit showing the typical appearance of LCIS. (C) At high magnification the lobular unit is seen to be distended and distorted by characteristically uniform, round tumor cells with bland nuclei. LCIS is usually diffusely dispersed throughout the breast and is often bilateral. Rarely producing a mass or abnormality on mammography, it is commonly discovered coincidentally during a biopsy performed for other suspicious lesions. Women with LCIS have a slightly higher risk of developing invasive cancer, whether ductal or lobular in origin, in their lifetime.
FIGURE 10.24 LOBULAR CARCINOMA IN SITU. High-power microscopic section shows clusters of tumor cells spreading along a duct in a “pagetoid” fashion; that is, displacing the normal ductal epithelium toward the lumen, which is lined by attenuated luminal surface cells. This should not be confused with Paget’s disease of the breast, a lesion of ductal origin, in which tumor cells extend into the epidermis (see Fig. 10.25).

FIGURE 10.25 PAGET’S DISEASE OF THE BREAST. In this unique clinical entity, one of the main ducts leading to the nipple becomes engorged with neoplastic cells. Clinically, patients present with an eczematous rash that extends to and involves the areola. This rare condition may or may not be associated with an underlying invasive carcinoma.

FIGURE 10.26 PAGET’S DISEASE OF THE BREAST. The irregular epidermis is infiltrated by characteristic cells with abundant pale-staining granular cytoplasm and large, oval, vesicular nuclei with prominent nucleoli.

FIGURE 10.27 INVASIVE DUCTAL CARCINOMA. Low- and high-power (inset) photomicrographs of a poorly differentiated adenocarcinoma show that the stroma is infiltrated by pleomorphic tumor cells showing a high mitotic rate. Note the necrosis and lack of tubule formation.
FIGURE 10.28 INVASIVE DUCTAL CARCINOMA. Low magnification of a breast biopsy specimen stained for estrogen receptor protein (ERP) using an estrogen receptor immunocytochemical assay (ERICA) shows that most cells are positive (brown). ERICA allows for semiquantitation of ERP. High magnification (inset) reveals that the antibody is localized to the nuclei (brown). (Courtesy of Dr. S.L. Khoury, Brigham and Women’s Hospital, Boston, MA.)

FIGURE 10.29 INVASIVE DUCTAL CARCINOMA. Photomicroscopic section of a breast biopsy specimen demonstrates an invasive ductal carcinoma in the lymphatic vessels of the breast parenchyma.

FIGURE 10.30 INVASIVE LOBULAR CARCINOMA. (A) The classic presentation of this tumor is marked by a “single-file” pattern of uniform malignant cells infiltrating the stroma. The invasive lesion surrounds foci of in situ tumor. (B) Single-file tumor cells surround an involved duct, producing a target-like pattern.
FIGURE 10.31 TUBULAR CARCINOMA. Low- and high-power (inset) microscopic sections of this histologic variant of invasive ductal carcinoma show tubular structures infiltrating the stroma. The lumina of the tubules are lined by a single cell layer of well-differentiated cells. This type of breast cancer has a better prognosis than common infiltrating ductal carcinoma.

FIGURE 10.32 MEDULLARY CARCINOMA. (A) Low-power photomicrograph of this histologic variant of invasive ductal carcinoma demonstrates its characteristic syncytial growth pattern. The tumor has a smooth, well-circumscribed border and shows a prominent lymphocytic infiltrate. (B) At higher magnification, the classic pleomorphic cells with bizarre nuclei are evident. This malignancy has better 5- and 10-year survival rates than common ductal carcinoma. (Courtesy of Dr. N. Weidner, Brigham and Women’s Hospital, Boston, MA.)
**FIGURE 10.33** MUCINOUS OR COLLOID CARCINOMA. (A) Low-power microscopic section shows islands of tumor cells within a sea of mucin. (B) Higher magnification demonstrates sharply circumscribed tumor aggregates with characteristic smooth borders and a homogeneous cell population. Pure histologic forms of this variant have better prognoses than common ductal carcinoma.

**FIGURE 10.34** CYSTOSARCOMA PHYLLOIDES. (A) The irregular cut surface of this tumor is marked by clefts that surround glistening gray to yellow islands of tumor intermixed with foci of necrosis (yellow). (B) Low-magnification study shows the classic leaflike projection of hypercellular stroma into a benign ductal structure. At high magnification (C), hypercellular areas demonstrate osteosarcomatous differentiation with osteoid (pink) deposition. Scattered “osteoclast-like” giant cells are also present. Typically, malignant stroma in these tumors appears fibro- or myxoliposarcomatous and less commonly like osteosarcoma, rhabdomyosarcoma, or chondrosarcoma. (Courtesy of Dr. N. Weidner, Brigham and Women’s Hospital, Boston, MA.)
FIGURE 10.35  (A) Assays for steroid hormone receptors. Scatchard analysis of [3H]estradiol binding to estrogen receptor (ER) in human breast cancer cytosol, determined by the multipoint Dextron coated charcoal (DCC) assay. The calculated binding affinity (K_d) and the quantitative receptor content are shown. (B) Localization of ERP using the ERICA assay (see Fig. 10.28). In this frozen section of an infiltrating ductal carcinoma, a brown stain in the nucleus defines the presence of ER. Although most cells in this tumor show immunoreactivity, there is heterogeneity in the degree of reactivity among the tumor cells.
Staging of Breast Cancer

T, Primary tumor

T0  No evidence of primary breast cancer
T1  Tumor ≤ 2 cm greatest dimension
T2  Tumor 2–5 cm greatest dimension
T3  Tumor > 5 cm greatest dimension
T4  Fixation to chest wall
    Edema, peau d'orange
    Ulceration of skin

N, Lymphatic spread

N0  No palpable regional lymph node
N1  Palpable ipsilateral axillary lymph node(s), movable
N2  Palpable ipsilateral axillary lymph node(s), fixed
N3  Metastases to ipsilateral/supraclavicular lymph node(s)
N2a  Metastasis to ipsilateral axillary lymph node(s) fixed to one another (matted) or to other structures
N2b  Metastasis only in clinically apparent (as detected by imaging studies [excluding lymphoscintigraphy] or by clinical examination or grossly visible pathologically) ipsilateral internal mammary nodes in the absence of evident axillary node metastases

MX  Distant metastases cannot be assessed

M0  No distant metastases
M1  Distant metastases present

Staging criteria for breast cancer, TNM classification

Primary tumor (T)
TX  — Primary tumor cannot be assessed
T0  — No evidence of primary tumor
Tis  — Carcinoma in situ
  • Tis (DCIS)  — Intraductal carcinoma in situ
  • Tis (LCIS)  — Lobular carcinoma in situ
  • Tis (Paget’s)  — Paget’s disease of the nipple with no tumor;
    tumor-associated Paget’s disease is classified according to
    the size of the primary tumor
T1  — Tumor 2 cm or less in greatest dimension
  • T1mic  — Microinvasion 0.1 cm or less in greatest dimension
  • T1a  — Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
  • T1b  — Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
  • T1c  — Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2  — Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3  — Tumor more than 5 cm in greatest dimension
T4  — Tumor of any size with direct extension to (a) chest wall or (b) skin,
    only as described below:
  • T4a  — Extension to chest wall
  • T4b  — Edema (including peau d’orange) or ulceration of the breast
    skin, or satellite skin nodules confined to the same breast
  • T4c  — Both (T4a and T4b)
  • T4d  — Inflammatory carcinoma

Note: Dimpling of the skin, nipple retraction, or any other skin change except those
described for T4b and T4d may occur in T1–3 tumors without changing the classification.

Regional lymph nodes (N)

N0  — Regional lymph node metastases cannot be assessed (e.g., previously removed)
N1  — Metastasis to movable ipsilateral axillary lymph node(s)
N2  — Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in
    clinically apparent ipsilateral internal mammary nodes in the absence
    of evident axillary node metastases
  • N2a  — Metastasis to ipsilateral axillary lymph node(s) fixed to one
    another (matted) or to other structures
  • N2b  — Metastasis only in clinically apparent (as detected by imaging
    studies [excluding lymphoscintigraphy] or by clinical examination or
    grossly visible pathologically) ipsilateral internal mammary nodes in
    the absence of evident axillary node metastases

Stage grouping of breast cancer

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(From AJCC Cancer Staging Manual, 6th ed., 2002.)
### FIGURE 10.37 OVERALL 5-YEAR SURVIVAL BY BREAST CANCER STAGE.


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### FIGURE 10.38 LYMPHATIC SPREAD OF BREAST CANCER.

Lymph node metastases are present at the time of diagnosis in up to 60% of cases. In general, lateral lesions in the breast metastasize to axillary and supraclavicular nodes, whereas medial tumors tend to metastasize to the internal mammary and mediastinal lymph nodes, as well as the supraclavicular nodes. However, lymph node involvement is merely a marker for the probability that the cancer has spread from the breast. A positive finding implies that microdeposits of breast cancer will probably be present in other areas as well.

### FIGURE 10.39 STAGE (T1N0)

**BREAST CANCER.** Magnified view of a screening mammogram from a 52-year-old woman who had no palpable mass demonstrates the classic clustered microcalcifications of several shapes and sizes highly suggestive of carcinoma. Some show linear branching, which is even more suggestive of a ductal lesion. Biopsy confirmed an early invasive ductal carcinoma. (Courtesy of Dr. P. Stomper, Roswell Park Memorial Institute, Buffalo, NY.)

### FIGURE 10.40 STAGE (T1N0)

**BREAST CANCER.** Magnified view of a mammogram from a 50-year-old woman with a history of “lumpy” breasts shows a 1.0-cm stellate mass in the superior portion of the breast. The lesion was excised and found to be an invasive ductal carcinoma. (Courtesy of Dr. P. Stomper, Roswell Park Memorial Institute, Buffalo, NY.)
FIGURE 10.41 STAGE IIA (T2N0) BREAST CANCER. This mammogram from a 65-year-old woman shows that the breasts are not too dense; therefore, the 2.5-cm stellate mass in the upper outer quadrant of the right breast was easily palpated. Histologic examination following resection showed an invasive ductal carcinoma.

FIGURE 10.42 STAGE IIIB (T4N0) BREAST CANCER. A 45-year-old woman presented with a very large (10 cm) primary tumor. There was an inflammatory component, but a distinct underlying mass was palpable and quite easily detected on the mammogram (A). (B) Following chemotherapy and radiation therapy the mass completely disappeared, replaced only by the distortion artifact left by the biopsy. Three months later the tumor recurred within the same breast. (C) The mammogram demonstrates multiple nodular tumor masses.
FIGURE 10.43   STAGE IIIB (T4) BREAST CANCER. A common presentation at this stage is retraction, dimpling, and thickening of the skin surrounding the nipple. This clinical finding is designated “peau d’orange,” a term deriving from the pitting and coloration of the skin that resembles orange peel.

FIGURE 10.44   STAGE IIIB (T4) BREAST CANCER. Classically, inflammatory breast cancer does not present as a discrete mass but instead as cutaneous erythema with overlying skin warmth, as illustrated in the left breast of this 63-year-old patient.

FIGURE 10.45   STAGE IIIB (T4) BREAST CANCER. Seven months after a normal baseline mammogram (A), a 35-year-old woman developed skin thickening and erythema of the breast. (B) At that time her mammogram demonstrated a diffuse increase in density—a characteristic finding in inflammatory breast cancer corresponding to the lack of a distinct mass. Biopsy confirmed the diagnosis of inflammatory breast cancer.
The clinical presentation of inflammatory breast cancer is sufficient to make a diagnosis. Yet pathologic confirmation of invasion of dermal lymphatics by malignant cells, as shown in this photomicrograph, can help distinguish this condition from benign mastitis. Note the absence of skin infiltration by inflammatory cells in cancer. The erythema and warmth observed clinically are due to obstruction of dermal lymphatics and subsequent cutaneous lymphedema.
FIGURE 10.49 RECURRENT BREAST CANCER. Locally recurrent disease can often present as very subtle subcutaneous nodules along the mastectomy scar or as a nodular cutaneous rash. This patient shows elements of both presentations. Biopsy revealed adenocarcinoma that resembled the primary carcinoma.

FIGURE 10.50 PROGRESSIVE BREAST CANCER. In a few patients with regional metastases, local problems become the main source of morbidity. Occasionally, as in the case of this 60-year-old patient (A), the subcutaneous nodules become confluent and extend across the chest wall, as well as laterally and posteriorly. This pattern of confluence has been designated an “en cuirasse” carcinoma. Advanced cancer has involved both breasts, resulting in “auto-mastectomies.” For most of the course of her illness this patient was plagued by a restriction in pulmonary function due to the bandlike distribution of metastases involving the chest wall. (B) Six months later the metastases had progressed despite therapy.

FIGURE 10.51 AXILLARY LYMPH NODE METASTASES. The presence of metastases to the axillary lymph nodes is the single most important prognostic factor in patients with primary breast cancer. (A) This lymph node with metastatic breast cancer shows only a small residual area of lymphoid tissue. (B) At higher magnification metastatic deposits can be seen in the subcapsular sinus, a common location for metastases.
FIGURE 10.52  SUPRACLAVICULAR/MEDIASTINAL METASTASES. A 35-year-
old woman who had undergone lumpectomy and radiation therapy for
stage I breast cancer 2 years previously presented with left-sided Horner’s
syndrome and was found to have a 1-cm hard, fixed nodule in the left
supraclavicular fossa. Her chest film demonstrated a soft tissue mass in the
left aortopulmonary window. CT scans of the upper thorax show a soft tissue
mass (A) filling the left supraclavicular fossa and (B) extending interiorly into
the left anterior mediastinum. There was no evidence of distant disease. It
was of interest that the primary lesion was located in the medial aspect of
the left breast, and axillary lymph nodes did not contain cancer. The pattern
of recurrence shown here probably represents metastasis to the internal
mammary lymph node chain.

FIGURE 10.53  FREQUENCY OF BREAST CANCER METASTASES. The most common
first sites of recurrent breast cancer are
the chest wall, the regional lymph nodes,
and/or bone. Liver, lung, and central
nervous system (CNS) are less common
sites of recurrence. In patients with well-
advanced disease, breast cancer can
be found in almost any organ. Autopsy
studies show that metastases are most
commonly found in the chest wall and in
the surrounding lymph nodes, as well as
in the bones, liver, lung, pleura, and CNS
(brain, spinal cord, meninges). Metastases
may also occur in gastrointestinal organs
(pancreas, stomach, large and small
intestines), endocrine organs (ovaries,
adrenals, pituitary, thyroid), and the
cardiovascular system (pericardium,
endocardium, myocardium).
FIGURE 10.55 LYTIC VERSUS BLASTIC BONE METASTASES. In general, lytic bone metastases are more common than osteoblastic lesions, although many patients show mixed lytic lesions with areas of osteoblastic reaction. (A) Diffuse lytic lesions can be seen in this patient’s right femoral head and ischial pubic ramus. Such lesions weaken the cortex, often resulting in pathologic fracture. (B) Radiograph of the pelvis of a 45-year-old woman demonstrates widespread foci of increased bone density representing osteoblastic activity surrounding bone metastases of breast cancer. It is interesting to note that effective therapy may alter the nature of lytic bone metastases, converting them to sclerotic, blastic lesions. For example, the CT scan demonstrated a large lytic region (arrow) with destruction of the right pedicle (C). At the same horizontal section following successful radiation therapy, the previously lytic area shows sclerosis and calcification (D).
Breast cancer can metastasize to the skull without involving the brain parenchyma. (A) Plain radiograph demonstrates large lytic metastases in the bones of the cranium. (B) CT scan of another patient who had a palpable posterior skull metastasis shows a soft tissue mass with extension through the thickness of the bone. Although the brain parenchyma was compressed posteriorly, the patient had no neurologic symptoms.
FIGURE 10.58  BONE MARROW METASTASES. Bone marrow metastases may develop with or without lytic or osteoblastic bone lesions. Anemia, leukopenia, thrombocytopenia, or various combinations of these may be the presenting clues to underlying intramedullary metastases. This low-power microscopic section of a bone marrow aspirate shows several clumps of malignant cells. At high power (inset) one clump of tumor cells demonstrates the characteristic features of metastatic carcinoma: a syncytial pattern or clumping of cells, the variable size and shape of tumor cells, and a high nucleus-to-cytoplasm ratio. The distinct, rather large, nucleoli seen here may not always be present. (Courtesy of P. Leavitt, Dana-Farber Cancer Institute, Boston, MA.)

FIGURE 10.59  LIVER METASTASES. Liver metastases of breast cancer are usually suspected in the presence of abnormal liver function tests or elevated circulating tumor markers (e.g., CEA or CA15-3). This CT scan demonstrates two very large metastases.

FIGURE 10.60  LIVER METASTASES. (A) CT scan of the abdomen in a 40-year-old patient shows multiple discrete lesions within the liver. (B) The response to chemotherapy can be impressive. After three courses of chemotherapy, the improvement in the patient’s liver is remarkable.
FIGURE 10.61 INTRATHORACIC METASTASES. Intrathoracic metastases can be manifested in several ways. Among the more common is malignant pleural effusion, as demonstrated by the large right effusion on this chest film (A); multiple metastatic pulmonary nodules are also evident. (B) Chest CT scan confirms the pleural effusion; in addition, the advanced right breast cancer can also be seen.

FIGURE 10.62 MALIGNANT PLEURAL EFFUSION. Pleural effusions are common in patients with breast cancer as a result of metastatic spread to the pleural surfaces or mediastinum. However, a correct diagnosis may require thoracocentesis with biochemical analysis and cytologic examination of pleural fluid. (A) Cytospin preparation from a malignant pleural effusion shows a cluster of highly pleomorphic breast cancer cells with distinct nucleoli. The surrounding cells are all normal mesothelial cells. (B) High-power view of a cytocentrifuge smear of pleural fluid shows a clump of large, bizarre, malignant cells with discrete nucleoli. (A, Courtesy of Dr. A. Lukacher, Brigham and Women’s Hospital, Boston, MA.)
FIGURE 10.63 Lymphangitic Metastases. Two years after undergoing a left modified radical mastectomy, a 59-year-old patient developed shortness of breath. (A) Her chest film shows a diffuse, nodular-interstitial pattern consistent with lymphangitic metastases. (B) Macroscopically, lymphangitic metastases (from a different patient) appear as multiple yellow lesions involving lymphatic vessels. (C) Microscopically, metastatic tumor cells can be observed filling these vessels.

FIGURE 10.64 Brain Metastases. Breast cancer commonly spreads to the brain, causing neurologic morbidity related to the specific site of involvement. Metastases can be single, multiple, or meningeval. (A) CT scan of the brain of a 62-year-old woman, who presented 6 years after having undergone a mastectomy and adjuvant chemotherapy for a stage II breast carcinoma, shows a well-circumscribed, enhancing lesion with surrounding edema in the left temporo-occipital region. She also had pulmonary and hepatic metastases. (B) Repeat CT scan taken 3 months after completion of successful radiation therapy reveals that the enhancing lesion is no longer evident and the edema has almost completely resolved. Her symptoms also totally resolved.
In addition to parenchymal CNS metastases, breast cancer can also spread to the leptomeninges. This 65-year-old woman with known metastatic breast cancer presented with a headache and multiple cranial nerve deficits. MRI without gadolinium was interpreted as normal (A, B). However, with gadolinium enhancement (C, D) the meningeal surface was found to be abnormally thickened (arrow). Lumbar puncture revealed the presence of metastatic breast cancer in the cerebrospinal fluid (E).
Occasionally breast cancer metastasizes to multiple organs simultaneously, resulting in complex syndromes that are diagnostically challenging. A 63-year-old patient presented 5 years after a left modified radical mastectomy with complaints of fatigue, malaise, nausea, vomiting, shortness of breath, and multiple areas of bony pain. In addition, she noted bruising, hematuria, and some blood in the stools. Physical examination revealed paleness and multiple petechiae and ecchymoses (A); she also had congestive heart failure and hepatomegaly. CT scan demonstrated diffuse hepatic metastases, and bone scan showed multiple sites of increased uptake. Her chest film was highly suggestive of lymphangitic carcinomatosis. Laboratory evaluation revealed pancytopenia, as well as hepatic and renal insufficiency. (B) Evaluation of a peripheral blood smear demonstrates a “red cell fragmentation syndrome” with numerous schistocytes and anisocytosis. Almost no platelets were seen, and the leukocyte count was low. She had microangiopathic hemolytic anemia. (C) Bone marrow core biopsy examination reveals almost complete replacement of hematopoietic elements with metastatic breast cancer cells, together with marked fibrosis. (D) At higher magnification, nests of tumor cells are seen forming tubular structures within a dense fibrous stroma. (E) Silver-stained section shows that the nests of tumor cells are surrounded by reticulin fibers. All the patient’s signs and symptoms could be related to widespread metastatic breast cancer.
FIGURE 1.67 CIRCULATING TUMOR MARKERS AS MONITORS OF DISEASE COURSE. The preceding figures have illustrated the importance of determining whether a patient is responding to therapy or whether her disease is progressing. History, physical examination, and radiographic tests can be very helpful in determining which of these is occurring. However, circulating tumor markers can also correlate with clinical disease course and can be useful in monitoring patients during therapy. In this figure, a patient with metastatic breast cancer to bone and lung (A) was initially treated with chemotherapy. Her symptoms began to resolve during the first 2 months of therapy, but interpretations of her physical examination, chest radiograph, and bone scans were equivocal (B). However, her CA15-3 levels decreased from an initial level of 200 U/mL to 50 U/mL. Her chemotherapy was continued, and by the fourth month of therapy she was found to be responding, as determined by history, bone scan, and chest radiography findings (C). Of note is that the patient’s CEA was never elevated and therefore in this patient was of no clinical utility.
(A) An incisional biopsy makes a definitive diagnosis.

(B) Excisional biopsies, though diagnostic, can also be therapeutic by eliminating the need for further breast surgery when radiation therapy is performed.

Cosmesis is best maintained using circular incisions in the upper half of the breast and radial incisions in the lower half of the breast.

The cosmetic results of conservative therapy are usually quite satisfactory. This 70-year-old patient had a stage I carcinoma of the left breast that was treated by excisional biopsy and primary irradiation. Although there is some asymmetry of the breast, as well as, on close inspection, some modest skin thickening and retraction due to the therapy, it is very difficult to determine which breast was treated.

The latissimus dorsi myocutaneous flap is based on the thoracodorsal artery and vein. This flap is rotated from the back and becomes the breast mound. (From Vasconez et al., 1991.) Alternatively, a transverse rectus abdominis muscle (TRAM) flap can be used, which is advantageous in large-breasted women when additional tissue coverage is needed.
FIGURE 10.72 (A) The resultant scar from harvesting a latissimus flap. (B, C) The resulting cosmetic effect after reconstruction with a latissimus flap.

FIGURE 10.73 Silicone implant (A) and tissue expander inflated with saline (B).
FIGURE 10.74 (A) A patient with bilateral mastectomies. (B, C) Frontal and side views of the same patient after bilateral silicone implants.

FIGURE 10.75 (A) Before mastectomy. (B) The same patient after mastectomy and TRAM flap reconstruction.

FIGURE 10.76 Stage I and II breast cancer can be treated by conservative therapy or mastectomy. This 46-year-old patient had stage II disease and underwent a left modified radical mastectomy followed by radiation therapy to the chest wall. L-phenylalanine mustard was then administered, resulting in a geometrically shaped area of hyperpigmentation and thickening of the chest wall due to a radiation recall reaction in the skin. Adjuvant radiation to the chest after mastectomy is no longer indicated in most patients. Although it decreases local recurrence, it does not affect survival and may be associated with significant morbidity.

FIGURE 10.77 A 64-year-old patient with significant arm edema after a radical mastectomy, full axillary dissection, and postoperative chest wall and axillary radiation therapy. The patient’s left arm is immensely swollen in contrast to her unaffected, normal right arm.
FIGURE 10.78  SENTINEL NODE BIOPSY.  (A) Axillary lymph mapping.  (B) Injection of blue dye in the tumor cavity.  (C) Identification of the sentinel node (follow blue line).
Fish + Cells have multiple HER2 genes and these genes lead to overexpression of HER2 protein

FIGURE 10.79 (A, B) There are two methods to determine HER2/neu status of tumors: immunohistochemistry and fluorescent in situ hybridization (FISH). HER2/neu overexpression is assessed by immunohistochemistry and is scored as 0, 1+, 2+, or 3+. Generally HER2/neu 2+ and above are considered positive. HER2/neu overamplification is assessed by FISH.

FIGURE 10.80 COMPLICATIONS OF CHEMOTHERAPY. Chemotherapy can also produce integumentary toxicity. This patient had metastatic breast cancer and was treated with high-dose doxorubicin. After her first course she noticed a change in her fingernails. She went on to develop onycholysis and onychomadesis. Although uncommon, this is a potential complication of doxorubicin.

FIGURE 10.81 RADIATION PNEUMONITIS. Radiation therapy can be associated with local tissue damage and toxicity. This patient presented with a T2N3 breast cancer with supravacuicular lymphadenopathy. She was treated by lumpectomy and radiation therapy to the breast, as well as radiation therapy to the supravacuicular fossa. At this time her chest radiograph was normal (A). Two years later the patient presented with a nagging, nonproductive cough and some dyspnea on exertion. A chest radiograph (B) demonstrated a nodular, right upper lobe density, and a CT scan (C) confirmed the presence of these apical nodules. Bronchoscopic evaluation failed to reveal any endobronchial lesions, and a fine-needle aspiration of this area was also nondiagnostic. Over the next 5 years the patient did not develop any progressive symptoms or signs of malignancy. Therefore, the changes were considered to be secondary to her prior radiation, which included the right pulmonary apex.
REFERENCES AND SUGGESTED READINGS

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**Figure Credits**

The following books published by Gower Medical Publishing are sources of figures in the present chapter. The figure numbers given in the listing are those of the figures in the present chapter. The page numbers given in parentheses are those of the original publication.


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