Chapter

23 Breast Cancer

Epidemiology

- Women older than 50 years (5% are younger than 40 years).
- Second most common cancer diagnosed in American women.
- More common in the United States than in the Eastern Hemisphere.
- One in eight to nine American women will develop breast cancer in her lifetime.

Risk Factors

- Factors known to increase risk include previous diagnosis with breast cancer or ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS) or atypical hyperplasia, nulliparity, late parity (first pregnancy after age 35 years), young age at menarche.
- Germline mutations in the **BRCA1** and **BRCA2** genes account for fewer than 10% of all breast cancers; however, the risk in individuals with these mutations is extremely high (35% to 70% cumulative risk up to age 60 years), and such women are given the option of prophylactic mastectomy plus/minus selective estrogen receptor modulators.
- Factors thought to increase risk but still controversial are smoking, inactivity/obesity during adolescence and young adulthood, hormone replacement therapy, and significant daily alcohol consumption.
- Primary prevention strategies proven to reduce mortality include annual mammography between ages 50 and 69 years; mammography before age 50 years in women without risk factors is often done, though not proven to change mortality.
- Self-breast examination and even clinical breast examination are not proven to reduce mortality.

Pathology

Fibroadenomas

- The most common benign breast tumors; usually located in the upper outer quadrant, they are well circumscribed and movable.
- Consist of both fibrous and glandular cells.

- Hormonal influences such as menses and pregnancy may influence size.

Phyllodes Tumors

- Arise from intralobular stroma of the breast and are usually benign.
- Cystosarcoma phyllodes is a malignant version that can behave more aggressively.

Intraductal Papillomas

- Arise from within ducts usually close to the nipple and are usually benign.
- They do often recur, and when they exist in groups, there is an increased risk of malignant transformation (papillocarcinoma).

***Ductal Carcinoma* In Situ**

- DCIS consists of malignant cells that do not invade the basement membrane of breast ducts.
- Of the five histologic subtypes, **comedocarcinoma** is considered high grade and predictive of recurrence.

***Lobular Carcinoma* In Situ**

- LCIS is characterized by a benign-appearing proliferation of terminal ducts and ductules that is often multifocal and bilateral.
- In untreated patients, more than 30% will develop invasive infiltrating ductal or lobular carcinoma in the affected or contralateral breast.

Infiltrating Ductal Carcinoma

- The most common breast cancer histology, accounting for about 75% of breast cancers.
- **Scirrhous** carcinoma is the most common subtype and is characterized by well-demarcated hard nodules consisting of cords and nests of malignant ductal cells.
- **Medullary** carcinoma is much less common and characterized by a lymphocytic infiltrate; these tumors have a better prognosis.
- **Mucinous** carcinoma is a more slow-growing subtype, often diagnosed in elderly women and on resection exhibits a gelatinous consistency.
- **Paget disease** is a subtype in which malignant ductal cells extend intraepithelially to the skin of the nipple.

Invasive Lobular Carcinoma

- Invasive lobular carcinoma constitutes only about 10% of breast cancers and like its noninvasive counterpart arises from terminal ductules of breast lobules.

- Tumor cells are often arranged in single files/strands, but at times it may be difficult to distinguish from ductal carcinomas.
- Many are multicentric within a breast and about 20% are bilateral.

Clinical Manifestations

History

- About 65% of patients will present with a breast lump.
- More patients are presenting with asymptomatic screening mammography abnormalities.
- Any complaints of skin changes overlying the breast or nipple, as well as nipple discharge, should be further evaluated (see later discussion).
- A full family history is very important and should include other cancer types.

Diagnostic Evaluation

- The diagnostic approach to a breast mass should start with the physical examination noting skin changes, nipple discharge, and adenopathy in the axillae and supraclavicular regions.
- The "triple screen" employs mammography, ultrasound, and fine needle aspiration (FNA) for further evaluation.
- If suspicion is high for the diagnosis of breast cancer and the patient is asymptomatic, relevant laboratories include liver studies with calcium and alkaline phosphatase to assess for liver and bony metastases, as well as a complete blood cell (CBC) count to assess for anemia and superimposing infection.
- Computed tomography (CT) scanning of the chest, abdomen, and pelvis and/or PET scan is used to evaluate for metastases if the patient is symptomatic or if the laboratory results are abnormal.
- Mammography is recommended in the contralateral breast before surgical intervention.
- MRI is particularly helpful in screening lobular carcinoma and BRCA1/2 carriers.
- If there is nothing to suggest distant metastases, the surgeons will resect the lesion with margins and perform a **sentinel node biopsy,** in which blue dye is injected into the tumor area; the first node to pick up the dye is resected and examined for malignant cells. The test has a 95% negative predictive value; that is, if no malignant cells are noted, the surgeons finish resection of the mass and do no further nodal removal.
- If the sentinel node biopsy is positive, or if there is evidence of stage III or greater disease, a formal axillary nodal dissection (removal of 10 to 15 nodes is performed).
- Many surgeons now routinely perform sentinel node biopsies even for DCIS.

Staging/Prognosis

- The American Joint Committee on Cancer TNM staging system is the most widely used for breast cancer.
- Survival in breast cancer appears to be inversely correlated to the number of axillary nodal metastases present.
- Relapse appears to be related to the number of nodal metastases as well.
- A summary of the staging system and approximate survival rates is outlined in Table 23-1.

Treatment

- **Breast-conserving therapy** has been proven safe and effective for DCIS and stage I/II tumors (<4 cm); sentinel lymph node biopsy is usually pursued to confirm localized disease.
  - Postoperative breast radiation (not to the nodes) is standard of care; it has been shown to reduce recurrence

TABLE 23-1 AJCC TNM Staging System for Breast Cancer

Stage	Description	Survival Rate
Stage I	Tumor ≤2 cm, no nodes	98% 5-yr survival
Stage IIA	One to three axillary nodes without primary breast tumor, or tumor ≤2 cm with one to three axillary lymph nodes, or tumor ≤2 cm with microscopic invasion of internal mammary node(s) by sentinel lymph node biopsy, or tumor 2 to 5 cm without nodal involvement	88% 5-yr survival
Stage IIB	Tumor 2 to 5 cm with one to three axillary nodes, or tumor >5 cm without extension into other organs or lymph nodes	76% 5-yr survival
Stage IIIA	No primary breast tumor but four to nine axillary lymph nodes affected, or tumor up to 5 cm with four to nine axillary nodes, or tumor >5 cm with up to nine axillary nodes or with macroscopic involvement of internal mammary node(s) (by examination or imaging)	56% 5-yr survival
Stage IIIB	Tumor of any size with direct extension into the skin or chest wall with/without nodes, or any tumor size with more than ten axillary lymph nodes or ipsilateral supraclavicular/ infraclavicular lymph node involvement	49% 5-yr survival
Stage IV	Distant metastases, including contralateral lymph node spread	16% 5-yr survival

  - Chemotherapy is not usually given for tumors smaller than 1 cm with negative nodes.
  - Adjuvant chemotherapy is recommended for tumors larger than 2 cm, tumors between 1-2 cms with unfavorable prognostic markers and in lymph node-positive patients.
  - Hormonal manipulation is suggested in estrogen receptor + (ER+), progesterone receptor + (PR+) tumors. Tamoxifen is offered to pre-menopausal women. An aromatase inhibitor is offered to post-menopausal women. There are three known aromatase inhibitors: Anastrazole (Arimidex), Letrozole (Femara), and Exemestane (Aromasin).
  - Mastectomy is suggested for tumors larger than 4 to 5 cm, followed by chemotherapy plus/minus x-radiation therapy.
  - Radiation is given to tumors larger than 5 cm and to women with more than four lymph nodes positive with cancer. Ongoing studies are accessing the benefit of radiation for local control in patients with less than four nodes positive.
- Neoadjuvant (preoperative) chemotherapy is recommended for patients with localized Stage III disease as an attempt to downstage tumors for surgical resection. There is a trend towards neoadjuvant chemotherapy in earlier stage disease in order to skrink the tumor for lumpectomy and to assess in vivo responsiveness to chemotherapy. This has not shown a survival advantage over adjuvant chemotherapy.
- Metastatic disease (Stage IV) is treated with many different modalities. It is **not** curable.
- Hormonal manipulation is preferred for ER+, PR+ disease not in visceral crisis.
  - Tamoxifen or aromatase inhibitors are considered.
  - Second line manipulations include switching to another aromatase inhibitor, Fulvestrant (Faslodex), or Progesterone (Megace).
- Chemotherapy is the only option in ER–, PR– disease. Usually single agent chemotherapy is the standard with various agents depending on the adjuvant chemotherapy given. Examples are Navelbine, Taxanes, Gemzar, Carboplantinum, and the pill Xeloda. Combination chemotherapy is given for visceral crises; for rapid control of tumor bulk.
- Her-2/neu disease represents a disease that is responsive to Herceptin, a monoclonal antibody directed against the Her-2/neu gene. Herceptin can be given in any stage and setting and is synergistic with many different chemotherapy agents.