BREAST CANCER

Breast cancer is the most common type of cancer and second only to lung cancer as a cause of cancer death in American women. The median age at diagnosis will be 61 years. Even *though the disease occurs more frequently in white women than any other ethnic group, the mortality rate is highest among African Americans.*

❖ ETIOLOGY

The etiology of breast cancer remains largely unknown though a number of factors have been associated with risk of developing the disease. Evidence also strongly suggests that breast cancer biology involves very complex interactions between sex hormones, genetic factors, environment, and lifestyle.

⇨ Intrinsic Components

Aside from gender, the variable most strongly associated with breast cancer is age as disease risk and incidence increase with age. Although the probability of developing breast cancer increases with age, more than half the risk occurs after 60 years of age. Both personal and family history can influence the risk of developing breast cancer. A first-degree relative (ie, mother or sister) with breast cancer is associated with a 3-fold increase in risk. A second-degree relative with breast cancer is associated with 1.5-fold increase in risk. Family members on the paternal side contribute to risk similar to the maternal side. Prior histories of cancers involving the uterus and ovary also appear to be associated with an increased risk of developing breast cancer.

A number of endocrine factors have been linked to an increased risk for breast cancer. Many of the risks relate to the total duration of estrogen exposure. Hence, early menarche (before age 12 years) and late menopause (after age 55 years) are associated with an increased risk of the disease. Long-term use of hormone replacement therapy and concurrent use of progestins appear to contribute to breast cancer risk. Use of postmenopausal estrogen replacement therapy in women with a history of breast cancer is generally contraindicated.

In the early 1990s, the BRCA1 gene (locus 17q21) was found to be mutated in a large percentage of hereditary breast and ovarian cancer patients. A second breast cancer gene, called BRCA2, has been mapped to chromosome 13. Since *BRCA1* and *BRCA2* are tumor suppressor genes, mutations or functional aberrations result in loss of key inhibitory activities of both proteins.

⇨ Extrinsic Components

Experimental and epidemiologic evidence suggest an association between breast cancer and a diet high in calories, fat, and cooked meats. Obesity in postmenopausal

women and distribution of body fat around the abdominal region also appear to increase the risk of breast cancer. This risk factor may be related, in part, to peripheral conversion of androgens to estrogens in adipose tissue.
Evidence also indicates a modest ingestion-dependent relationship between alcohol and breast cancer. While exercise may have a modest protective effect against breast cancer, neither cigarette smoking nor breast augmentation (augmentation mammoplasty) appears to modify disease risk. Radiation is also associated with an increased risk of breast cancer. On the other hand, it is currently accepted that exposure to radiation doses utilized in diagnostic x-rays, including screening mammography, are not of clinical concern.

❖ CLINICAL PRESENTATION AND DIAGNOSIS

⇨ Early Detection

The rationale for early detection of breast cancer is based on the clear relationship between early stage disease at diagnosis and greater probability of long-term survival.
Common early signs and symptoms include:
-Painless lump (90% of cases) that is:
•• Solitary
•• Unilateral
•• Solid
•• Hard
•• Irregular
•• Non tender
-Stabbing or aching pain (10% of cases) as the first symptom
-Uncommon early signs and symptoms include:
•• Nipple discharge (3% of women and 20% of men), retraction, or dimpling
•• Eczema appearance of the nipple (Paget carcinoma)
•• Prominent skin edema, redness, warmth, and induration of the underlying tissue (inflammatory carcinoma)
-Metastatic signs and symptoms—tissues most commonly involved with metastases are lymph nodes (other than axillary or internal mammary), skin, bone, liver, lungs, and brain. The following symptoms of metastases will be present in about 10% of patients when they first seek treatment:
•• Bone pain
•• Difficulty breathing
•• Abdominal enlargement
•• Jaundice
•• Mental status changes

⇨ **Diagnosis**

Unless following up on abnormalities found during screening (breast self-examination), the initial workup for women presenting with signs or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional mammography, and possibly other imaging techniques such as magnetic resonance imaging. Most (80%–85%) breast cancers are visualized on a mammogram as a mass, a cluster of calcifications, or a combination of both. A breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

⇨ **Clinical Staging**

Stage is determined by primary tumor size (T), axillary lymph node involvement (N), and presence or absence of distant metastases (M). Simplistically, stage I disease is represented by tumors less than 2 cm in diameter and usually no lymph node involvement. *Stage I and II disease* (40% and 40% respectively of total cases) *is referred to as early breast cancer, which carries a relatively good prognosis and correlates with the highest probability of cure.* Stage III, or locally advanced breast cancer, has poorer disease features, including larger tumor size, positive node involvement, and tumor invasion of the chest wall. Stage IV disease is characterized by the presence of metastases (M_1) to organs or tissue distant from the primary tumor and is often referred to as advanced or metastatic breast cancer.

- ***EARLY BREAST CANCER***

❖ **TREATMENT**

⇨ **Desired Outcome**

Most patients presenting with invasive breast cancer today have small tumors with negative lymph nodes (stage I), or a stage II cancer. The goal of therapy for early breast cancer is cure. While surgery alone may be able to cure approximately one-third to one-half of all patients with early stage breast cancer, certain tumor features warrant addition of systemic therapy.

⇨ **Local-Regional Therapy**

Less aggressive surgical options for early invasive breast cancer include total mastectomy and breast conserving surgery (BCS) such as lumpectomy. Equally important is the issue related to complete axillary lymph node dissection (CALND). Because of the morbidity associated with the procedure, clinical trials were conducted to determine when biopsy of the sentinel lymph nodes was sufficient.

Except for the elderly and patients with substantial comorbid medical conditions, radiation therapy is an integral adjunct to BCS. However, radiation therapy should also be considered in certain post mastectomy situations, especially in patients with

more than three positive nodes or patients with positive sentinel nodes without CALND.

⇨ Systemic Adjuvant Therapy

Systemic adjuvant therapy is treatment that follows definitive local therapy when there is no evidence of disease beyond the axillary nodes but a high likelihood of disease recurrence. Hence, administration of systemic therapy (at a time when the tumor burden is low) should theoretically increase the likelihood of cure and minimize the emergence of drug-resistant tumor cell clones. *Most published results confirm that chemotherapy (in selected patients), hormonal therapy (in patients with hormone receptor–positive disease), anti-HER2 therapy (in tumors with amplification or overexpression of HER2) or appropriate combinations of these therapies improved disease free survival (*DFS*) and/or overall survival (OS) in patients with early-stage breast cancer.*

»» *Adjuvant Chemotherapy*

Cytotoxic drugs that have been used most frequently as adjuvant therapy of breast cancer include cyclophosphamide, anthracyclines (doxorubicin, epirubicin and liposomal doxorubicin), taxanes (paclitaxel and docetaxel), methotrexate, and fluorouracil. Chemotherapy is usually initiated within 3 weeks of the surgical procedure. Traditionally, treatment consisted of four to six cycles; and completed in less than 6 months.

It is generally agreed that patients with luminal B, HER2-positive, and basal-like subtypes should receive chemotherapy (both anthracycline and taxane) with hormonal and/or HER2-targeted therapy if indicated.

Examples of common chemotherapy regimens for breast cancer:

1- Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for four cycles

2- Fluorouracil 500 mg/m^2 IV, days 1 and 4
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for six cycles

3- Cyclophosphamide 600 mg/m^2 IV, day 1
Doxorubicin 60 mg/m^2 IV bolus, day 1
Fluorouracil 600 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for six cycles

4- Fluorouracil 500 mg/m^2 IV, day 1
Epirubicin 100 mg/m^2 IV bolus, day 1

Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycle every 21 days for six cycles
5- Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days
or
Paclitaxel 80 mg/m^2/week IV over 1 hour
Repeat dose every 7 days

»» ***Adjuvant Anti-HER2 Therapy***

HER-2 amplification or overexpression is found in approximately 15% to 20% of all breast cancers. Because of its aggressive features, trastuzumab (plus chemotherapy) is usually indicated in this subset of patients, especially for tumors greater than or equal to 0.5 cm in size. Most experts also agree that HER2-positive tumors appear to derive greater benefit from anthracycline or taxane-based chemotherapy regimens. When used with these agents, trastuzumab is given either following completion of the anthracycline or concurrently with the taxane. Current evidence indicates that the duration of trastuzumab therapy is 12 months.

»» ***Adjuvant Endocrine Therapy***

Estrogen and progesterone receptors (ER and PR) are cytoplasmic proteins that bind to nuclear DNA and function as transcription factors. Approximately 50% to 70% of patients with primary and metastatic breast cancer have hormone receptor–positive tumors. However, receptor-positivity refers to tumors expressing both ER and PR, as well as either ER or PR alone.

Hormonal therapies that have been studied in the treatment of early breast cancer include selective estrogen receptor modulators (SERMs, tamoxifen), ovarian suppression (surgical and pharmacologic), and the aromatase inhibitors (AIs).

Tamoxifen, has been used in the adjuvant setting for nearly four decades. Analysis of long-term data indicates the drug's antagonist (anti-estrogen) effect was associated with a significant reduction in disease recurrence and mortality. This observation, coupled with evidence of the drug's beneficial agonist activity on the lipid profile and bone density supported tamoxifen's role as standard endocrine therapy. However, the agonist properties are also associated with detrimental effects on endometrial tissue and blood coagulation.

In premenopausal women, tamoxifen alone is considered the adjuvant hormonal therapy of choice. Tamoxifen is initiated shortly after surgery or as soon as pathology results are known. However, when chemotherapy is also indicated, tamoxifen is given after all cytotoxic agents have been completed. Treatment with adjuvant tamoxifen (20 mg/day) has historically been for 5 years.

Expert panels strongly recommend AIs for postmenopausal women with hormone-dependent breast cancer. Although 5 years of adjuvant AI therapy is considered standard, there is also strong support for continuing hormonal therapy (beyond 5 years) if tamoxifen was used initially, especially in patients with high-risk features such as node-positive disease. AI therapy is associated with several adverse effects, including hypercholesterolemia, atherosclerotic cardiovascular disease, and skeletal-related events. The three available AIs are anastrozole (1 mg/day PO), letrozole (2.5 mg/day PO), and exemestane (25 mg/day PO).
Other endocrine therapies used for metastatic breast cancer include LHRH analogues (goserelin, leuprolide and triptorelin), Progestins (megestrol acetate and medroxy-progesterone) and Androgens (fluoxymesterone).

- ***LOCALLY ADVANCED BREAST CANCER (STAGE III)***

Locally advanced breast cancer is defined by tumors greater than or equal to 5 cm and a high likelihood of nodal involvement in the absence of demonstrable distant metastasis.
Treatment of stage III breast cancer consists of all modalities used in the management of early breast cancer. *The goal of therapy* is to achieve optimal systemic control of the disease. However, despite treatment, systemic relapse and death are common even when local-regional control is accomplished. One major difference related to the systemic therapies is the use of chemotherapy plus ant-HER2 therapy (if indicated) or hormonal therapy before surgery. This approach, referred to as neoadjuvant therapy, can render initially inoperable tumors resectable, even with the possibility of BCS. It is also conceivable that earlier administration of systemic therapy could have therapeutic benefits beyond surgical resection.

PROSTATE CANCER

Prostate cancer is the most commonly diagnosed cancer in US men and the second leading cause of cancer-related death in men. The disease course varies from a slow growing, asymptomatic tumor that may not require treatment to a rapidly progressing, aggressive tumor resulting in distant metastasis, morbidity, and mortality.

❖ ETIOLOGY

The widely accepted risk factors for prostate cancer are age, race, and family history of prostate cancer.

⇨ Age

Age is the greatest predictor of risk, the disease is rare under the age of 40, but the incidence sharply increases with each subsequent decade of life. Men of older age have had a greater lifetime exposure to testosterone, a known growth signal for the prostate.

⇨ Race

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidence of prostate cancer, but the disease is less common in Japan and other Asian countries. African Americans have a higher incidence and death rate.

The combination of increased testosterone and increased androgen receptor activation may account for the increased risk of prostate cancer in African American men.

⇨ Family History

Men with a brother or father with prostate cancer have twice the risk for prostate cancer compared to the rest of the population. Male carriers mutations of *BRCA1* and *BRCA2* are known to have an increased risk for developing prostate cancer.

⇨ Diet

Increased risk associated with high-meat and high-fat diets. Decreased intake of 1,25-dihydroxyvitamin D, lycopene, and β-carotene increases risk. Dietary factors that are potentially protective for prostate cancer include retinol, carotenoids, lycopene, calcium, and vitamin D consumption. Tomatoes, pink grapefruit, and watermelon are rich in lycopenes, antioxidants that help prevent damage to DNA.

⇨ Other Factors

Benign prostatic hyperplasia (BPH) is a common problem among elderly men, affecting more than 40% of men older than the age of 70 years. Because prostate cancer affects a similar age group and often has similar presenting symptoms(urinary hesitancy and frequency), the presence of BPH often complicates the diagnosis of prostate cancer, although it does not appear to increase the risk of prostate cancer.

Smoking has been associated with an increased risk of aggressive prostate cancer and smokers with prostate cancer have an increased mortality resulting from the disease compared with nonsmokers with prostate cancer.

❖ SCREENING

Digital rectal examination (DRE) has been recommended since the early 1900s for the detection of prostate cancer. The primary advantage of DRE is its specificity, reported at greater than 85%, for prostate cancer. Other advantages of DRE include low cost, safety, and ease of performance. However, DRE is relatively insensitive and subject to interobserver variability.

Prostate-specific antigen (PSA) is a useful marker for detecting prostate cancer at early stages, predicting outcome for localized disease, monitoring disease-free status, and monitoring response to treatment of advanced-stage disease. Periodic PSA monitoring is used widely for prostate cancer screening, with simplicity as its major advantage and low specificity as its primary limitation. Although PSA is often elevated in men with prostate cancer, the PSA may also be elevated in men who are smokers or with acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as BPH, a common condition in men at risk for prostate cancer.

Gland architecture is examined and then rated on the Gleason scale of 1 (well differentiated) to 5 (poorly differentiated). Two different specimens are examined, and the score for each specimen is added. Groupings for total Gleason score are 2 to 4 for well differentiated, 5 or 6 for moderately differentiated, and 7 to 10 for poorly differentiated tumors. Poorly differentiated tumors grow rapidly (poor prognosis), while well differentiated tumors grow slowly (better prognosis).

❖ CLINICAL PRESENTATION OF PROSTATE CANCER

⇨ Localized Disease

Asymptomatic

⇨ Locally Invasive Disease

Ureteral dysfunction, frequency, hesitancy, and dribbling
Impotence

⇨ Advanced Disease

Back pain
Cord compression
Lower extremity edema
Pathologic fractures
Anemia
Weight loss

❖ TREATMENT

⇨ Desired Outcome

The desired outcome in early stage prostate cancer is to minimize morbidity and mortality from prostate cancer with consideration that some degree of morbidity may be caused by the toxicity of treatment. Early stage disease may be treated with surgery, radiation, or observation. Although surgery and radiation are curative, they are associated with significant morbidity and a low rate of mortality. Advanced prostate cancer (metastatic spread) is not curable, and treatment of advanced disease should focus on providing symptom relief and maintaining quality of life.

⇨ General Approach to Treatment

The initial treatment for prostate cancer depends on the disease stage, Gleason score, presence of symptoms, and life expectancy of the patient.

For asymptomatic patients, determining risk for disease progression and recurrence are critical for determining treatment options. Asymptomatic patients with a low risk of recurrence, those with a T_1 or T_{2a} tumor, with a Gleason score of 2 through 6, and a PSA of less than 10 ng/mL (10 mcg/L) may be managed by active surveillance. However, radiation or radical prostatectomy may also be offered.

Individuals with T_{2b} disease or a Gleason score of 7 or a PSA ranging from 10 to 20 ng/mL (10 to 20 mcg/L) are considered at intermediate risk for prostate cancer recurrence. Individuals with less than a 10-year expected survival may be offered observation, radiation therapy, or radical prostatectomy with or without a pelvic lymph node dissection, and those with a greater than or equal to 10-year life expectancy may be offered either radical prostatectomy with or without a pelvic lymph node dissection or radiation therapy.

The patients at high risk of recurrence (stages T_{2c}, a Gleason score ranging from 8 to 10, or a PSA value greater than 20 ng/mL [20 mcg/L]) should be treated with androgen deprivation therapy for 2 to 3 years combined with radiation therapy. Patients with T_{3b} and T_4 disease have a very high risk of recurrence and are usually not candidates for radical prostatectomy because of extensive local spread of the disease.

Androgen deprivation with a GnRH agonist should be used with radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone.

Androgen deprivation therapy, with either orchiectomy, a GnRH agonist alone or a GnRH agonist plus an antiandrogen (combined androgen blockade), can be used to provide palliation for patients with advanced prostate cancer. Secondary hormonal manipulations, cytotoxic chemotherapy, immunotherapy, or supportive care is used for patients who progress after initial therapy.

⇨ Nonpharmacologic Therapy

»» ***Observation***

Observation or active surveillance involves monitoring the course of disease and initiating treatment if the cancer progresses or the patient becomes symptomatic. A PSA and a DRE are performed every 6 months with a repeat biopsy at any sign of disease progression.

»» ***Orchiectomy***

Bilateral orchiectomy, or removal of the testes, rapidly reduces circulating androgens to castrate levels (ie, serum testosterone levels less than 50 ng/dL [1.74 nmol/L]). However, many patients find this procedure psychologically unacceptable, and others are not surgical candidates.

»» ***Radiation***

The two commonly used methods for radiation therapy are external-beam radiotherapy and brachytherapy. Radiation therapy may be used to treat local or locally advanced prostate cancer with curative intent. In later stages of disease short courses of external beam radiation therapy can be used to palliate symptoms.

»» ***Radical Prostatectomy***

Radical prostatectomy is performed in patients who are surgical candidates with disease that requires definitive therapy based on risk factors and patient preference; additionally, the disease must be amenable to complete surgical resection.

Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; 50% to 80% regain sexual potency within the first year. Acute complications from radical prostatectomy and radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence). Chronic complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.

⇨ Pharmacologic Therapy

»» ***Gonadotropin-Releasing Hormone Agonists***

GnRH agonists are a reversible method of androgen deprivation and are as effective as orchiectomy in treating prostate cancer. Currently available GnRH agonists include leuprolide, leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant, and goserelin acetate implant. Leuprolide acetate is administered once daily, whereas leuprolide depot and goserelin acetate implant can be administered once monthly, once every 12 weeks, or once every 16 weeks (leuprolide depot).

The most common adverse effects reported with GnRH agonist therapy include vasomotor symptoms such as hot flashes, erectile impotence, decreased libido, and injection site reactions. Long-term adverse effects include decreased bone mineral density and metabolic syndrome. Disease flare-up in the first weeks of therapy can be caused by an initial induction of LH and FSH by the GnRH agonist, leading to an initial phase of increased testosterone production. It manifests clinically as an exacerbation of disease-related symptoms, usually increased bone pain or urinary symptoms.

»» ***Gonadotropin-Releasing Hormone Antagonists***

An alternative to GnRH agonists is the GnRH antagonist, degarelix. Degarelix reversibly binds to GnRH receptors on cells in the pituitary gland, reducing the production of testosterone to castrate levels. The major advantage of direct GnRH antagonists is the speed at which they can achieve the drop in testosterone levels; castrate levels are achieved in 7 days or less with degarelix, compared with 28 days with leuprolide, eliminating the tumor flare seen and need for antiandrogens with GnRH agonists.

Degarelix is equivalent to leuprolide in lowering testosterone levels for up to 1 year and is approved by the FDA for the treatment of advanced prostate cancer. Degarelix is available as 40-mg/mL and 20-mg/mL vials for subcutaneous injection, and the starting dose is 240 mg followed by 80 mg every 28 days. The starting dose should be split into two injections of 120 mg.

The most frequently reported adverse reactions are injection site reactions, including pain (28%), erythema (17%), swelling (6%), induration (4%), and nodule (3%). Similar to other methods of androgen deprivation therapy, osteoporosis may develop, and calcium and vitamin D supplementation should be considered. Degarelix is not approved in combination with antiandrogens.

»» Antiandrogens

The first generation of nonsteroidal antiandrogens includes: flutamide, bicalutamide, and nilutamide. Monotherapy with first-generation antiandrogens is less effective than GnRH agonist therapy. Therefore, for advanced prostate cancer, all currently available antiandrogens are indicated only in combination with androgen-deprivation therapy, flutamide and bicalutamide are indicated in combination with a GnRH agonist, and nilutamide is indicated in combination with orchiectomy. Enzalutamide is a second-generation antiandrogen that is indicated in metastatic castrate-resistant prostate cancer.

The most common antiandrogen-related adverse effects are gynecomastia, hot flushes, GI disturbances (diarrhea), liver function test abnormalities and breast tenderness.