KEY POINTS

- Precision medicine refers to agents that target specific mutations or alterations that are driving growth and survival in a particular tumor.
- Tumor markers of mutations or alterations can be inclusionary, in that they include a patient in a therapy that otherwise might not be considered, or exclusionary, in that they exclude a patient from a treatment that otherwise might have been used.

Immunotherapy

Immunotherapy agents are drugs that do not attack the cancer directly but rather mobilize the patient's own immune system to do so. This has become possible through the identification of immune checkpoints, which serve as "brakes" on the immune system in order to prevent the immune system from attacking itself and causing autoimmune diseases. Antibodies that block these checkpoints release the brakes on the immune system and allow it to aggressively attack the tumor. Adverse effects are related to resultant autoimmunity from the less-regulated immune system and can be severe. The first immune checkpoint identified was the antigen-4 (A-4) molecule on the surface of the cytotoxic lymphocyte (T cell), hence its designation cytotoxic T-lymphocyte antigen-4. Antibodies that block cytotoxic T-lymphocyte antigen-4, such as ipilimumab, have been successful in mobilizing the immune system against melanoma, renal cell carcinoma, and other malignancies. The other immune checkpoint that has been successfully exploited is the programmed death 1 (PD-1) receptor. Anti-PD-1 agents, such as nivolumab or pembrolizumab, have shown substantial and durable activity against melanoma and non-small cell lung cancers, as well as other tumors. Agents against the ligand of PD-1, PD-L1, such as atezolizumab or durvalumab, have also shown important clinical activity. Combinations of these agents are showing further effectiveness but with increased toxicity and also considerable expense. Many other checkpoints in the immune system are now being explored by numerous drugs in development.

Further progress in immunotherapy has occurred in the use of cellular immunity, particularly the development and commercialization of chimeric antigen receptor T cells, which have demonstrated striking activity in selected B-cell leukemias and lymphomas, albeit with substantial clinical and financial toxicity. Investigations into development of this technology for other liquid and some solid tumors are ongoing.

KEY POINT

- Immune checkpoints prevent the immune system from attacking both normal tissues (self) and malignant cells; immunotherapy can take advantage of this process by inhibiting the checkpoints and allowing the immune system to aggressively attack cancer cells.

Breast Cancer

Introduction

Breast cancer is the most common type of cancer in women in the United States, excluding skin cancers. In 2019, there were approximately 268,600 new invasive breast cancer cases and 48,100 in situ cases diagnosed. The lifetime risk of developing invasive breast cancer is 12.4% (about 1 in 8) for women in the United States. There were an estimated 40,610 deaths from breast cancer in the United States in 2017–the second leading cause of cancer death in women. The lifetime risk of dying from breast cancer for women in the United States is 2.76%. Breast cancer is rare in men.

Epidemiology and Risk Factors

Breast cancer incidence increases with age. The median age of diagnosis in women is 61 years. Incidence rates are highest in non-Hispanic White and Black women. Other risk factors for breast cancer are listed in **Table 2**.

Patients with deleterious *BRCA1* or *BRCA2* gene mutations have a 50% to 85% lifetime risk of breast cancer. Patients who received chest wall irradiation between ages 10 and 30 years for treatment of Hodgkin lymphoma have a 30% to 50% risk of breast cancer. Atypical breast lesions, such as atypical hyperplasia or lobular carcinoma in situ, result in a cumulative 30-year breast cancer risk of up to 35%.

Patients with possible hereditary breast cancer syndromes should be referred to a genetic counselor for assessment and possible genetic testing. The U.S. Preventive Services Task Force recommends assessment of women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or those who have a family history of *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Validated tools are available at https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. The National Comprehensive Cancer Network criteria for genetic testing are outlined in **Table 3**.

KEY POINTS

- Breast cancer incidence increases with age, with the highest incidence in non-Hispanic White women and second highest in Black women.
- Women with possible hereditary breast cancer syndromes should be referred to a genetic counselor for possible genetic testing for breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*.

Chemoprevention and Other Risk Reduction Strategies

Breast cancer screening for average-risk women is discussed in General Internal Medicine 2. The American

TABLE 2. Breast Cancer Risk Factors

Breast Cancer Risk Factor Category	Breast Cancer Risk Factors	Increase in Breast Cancer Risk or Lifetime Breast Cancer Risk
Reproductive factors	Early menarche, late menopause, first full-term pregnancy after age 30 years, nulliparity	RR, 1.2-3.5
Lifestyle	Obesity (BMI ≥30), lack of regular exercise, alcohol intake	RR, 1.2-1.6[a,b,c]
Treatment related: radiation	Prior chest wall irradiation in patients younger than 30 years (e.g., mantle irradiation for Hodgkin lymphoma)	RR, 5.0[d]
Treatment related: HRT	Combination estrogen and progesterone HRT after menopause	RR, 1.2-1.4[a]
Breast density[e]	Increased breast density	Risk increases with each category of breast density; for ≥75% density, RR is 4.7 compared with <10% density[f]
Atypical breast lesions	Atypical ductal or lobular hyperplasia, LCIS	RR, 3.8-5.3[g] RR, 5.4-8.0[h]
Family history of breast cancer and familial breast cancer syndromes	*BRCA1/2* mutation represents the most common familial breast cancer syndrome (5%-10% of all breast cancer tumors); others are rare	RR, 3.0-7.0

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; RR = relative risk.

[a]Data from Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001 Jan 25;344 (4):276-85. Erratum in: N Engl J Med. 2001 Jun 7;344(23):1804. [PMID: 11172156]

[b]Data from Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. [PMID: 21113759]

[c]Data from Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013 Feb;24(2):301-8. [PMID: 22910838] and Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998 Feb 18;279(7):535-40. [PMID: 9480365]

[d]Data from Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

[e]Breast density refers to the amount of radiologically dense breast tissue appearing on a mammogram.

[f]Data from Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. [PMID: 17229950]

[g]Data from Degnim AC, Visscher DW, Berman HK, et al. Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007 Jul 1;25(19):2671-77. [PMID: 17563394] and Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997 May;6(5):297-301. [PMID: 9149887]

[h]Data from Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long-term risk of breast cancer and relation to other factors. Cancer. 1996 Sep 1;78(5):1024-34. [PMID: 8780540]

TABLE 3. Highlights of NCCN[a] Recommendations for Breast and Ovarian Cancer Syndrome Genetic Testing

Individuals with a Personal History of Breast or Ovarian Cancer
Breast cancer diagnosed at or before age 45 years
Breast cancer diagnosed at age 46-50 years with one or more relatives[b] with breast, ovarian, prostate, or pancreatic cancer at any age
Women with two primary breast cancers, with the first diagnosed at or before age 50 years
Breast cancer diagnosed at any age with one or more relatives[b] diagnosed with ovarian cancer, breast cancer diagnosed at or before age 50 years, male breast cancer, metastatic prostate cancer, pancreatic cancer
Triple-negative breast cancer[c] diagnosed at or before age 60 years
Breast cancer in women of Ashkenazi (Eastern European) Jewish ancestry
Men with breast cancer diagnosed at any age
Ovarian cancer diagnosed at any age
Individuals without a Personal History of Breast or Ovarian Cancer
Family history of a known deleterious *BRCA1/2* mutation
BRCA1/2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type
Any individual with one or more first- or second-degree relatives meeting the above criteria

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; NCCN = National Comprehensive Cancer Network; USPSTF = U.S. Preventive Services Task Force.

[a]Full testing guidelines can be accessed at https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

[b]First-, second-, or third-degree relatives on the same side of the family.

[c]Negative for estrogen and progesterone receptors and *HER2* amplification.

TABLE 4. American Cancer Society Recommendations for MRI Breast Cancer Screening

Women with *BRCA1/2* mutations
Women who are a first-degree relative of a *BRCA1/2* carrier but are untested[a]
Women with a strong family history of breast cancer with a lifetime breast cancer risk of ≥20% to 25% as calculated by models[b] largely dependent on family history
Women who had radiation to the chest wall between ages 10 and 30 years (e.g., mantle radiation therapy for Hodgkin lymphoma)
Women with a history of other rare familial breast cancer syndromes

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes.

[a]Testing for the *BRCA1* or *BRCA2* mutation that is present in the family is strongly recommended, but some patients decide to defer testing. In this situation when their carrier status is unknown, breast MRI screening is recommended. If they are later tested and do not carry the mutation, MRI screening should be stopped.

[b]Models that can be used to estimate lifetime risk of breast cancer to determine if MRI screening is appropriate (please note that the Gail Model is not recommended for this use):

- BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- Claus model: Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first-degree family history of ovarian cancer. Breast Cancer Res Treat. 1993 Nov;28(2):115-20. [PMID: 8173064]
- Tyrer-Cuzik (also called IBIS Breast Cancer Risk Evaluation Tool): www.ems-trials.org/riskevaluator/

Cancer Society recommends screening certain women at high risk using annual mammography and breast MRI (**Table 4**).

The National Comprehensive Cancer Network recommends that women with a 5-year risk of breast cancer of 1.67% or greater are candidates for breast cancer chemoprevention with antiestrogens. A recommended tool for estimating 5-year and lifetime risks of breast cancer is the Gail Model Risk Assessment Tool (https://www.cancer.gov/bcrisktool/). All patients with atypical hyperplasia or lobular carcinoma in situ are candidates for chemoprophylaxis. Contrary to the National Comprehensive Cancer Network, the U.S. Preventive Services Task Force advises against using any hard cut-off point for defining increased risk but suggests focusing instead on each woman's values and priorities in weighing the reduced risk of breast cancer with increased likelihood of adverse effects.

Tamoxifen and raloxifene are selective estrogen receptor modifiers that block estrogen uptake in breast tissue. Exemestane and anastrozole are aromatase inhibitors that prevent the conversion of androgens into estrogens. These agents proportionally decrease the risk of breast cancer by 28% to 65% and are given for 5 years. **Table 5** summarizes these chemoprophylaxis options.

For women with *BRCA1* or *BRCA2* mutations, breast cancer screening with breast MRI should start at age 25 years and with mammography added at age 30 years. Prophylactic bilateral mastectomies for *BRCA1* or *BRCA2* mutation carriers decrease the risk of breast cancer by greater than 90%, whereas prophylactic bilateral salpingo-oophorectomy decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and all-cause mortality to age 70 years by 77%. Premenopausal prophylactic bilateral salpingo-oophorectomy also decreases the risk of breast cancer by 50% and is recommended after completion of childbearing.

KEY POINTS

- Women at high risk for breast cancer should be screened with annual mammography and breast MRI; this includes women with gene mutations who have a high risk of breast cancer including *BRCA1* or *BRCA2*, women with a strong family history of breast cancer, and those with a history of chest irradiation at a young age.
- Women with an elevated 5-year risk of breast cancer or with lobular carcinoma in situ or atypical hyperplasia should be considered for breast cancer chemoprophylaxis.
- Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy.

Staging and Prognosis of Early-Stage Breast Cancer

Breast cancer staging and prognosis are presented in **Table 6**. In addition to the excellent prognosis for patients with small tumors with neither lymph node involvement nor distant metastases, the presence of hormone receptors and absence of human epidermal growth factor 2 (*HER2*) overexpression also favorably affect prognosis. Hormone receptor positivity also predicts risk reduction from antiestrogen therapy. Monoclonal antibodies such as trastuzumab that block *HER2* receptors are effective therapies and have markedly improved the prognosis for those with *HER2*-positive breast cancer.

For asymptomatic patients with newly diagnosed stage 0 to II (early-stage) breast cancer, current guidelines recommend against using imaging studies such as PET, CT, bone scan, or measuring serum markers such as CA15-3 or CA27-29, for staging, as the incidence of asymptomatic metastases is low. However, imaging studies for staging are recommended in patients with stage III disease or in those with earlier-stage disease who have signs or symptoms suggestive of metastatic disease.

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TABLE 5. Primary Chemoprevention for Breast Cancer

Considerations	Tamoxifen	Raloxifene	Exemestane	Anastrozole
Mechanism of action	SERM	SERM	Aromatase inhibitor	Aromatase inhibitor
Breast cancer risk reduction	43% at 7 years[a] 28% at 10 years[b]	As effective as tamoxifen at reducing the risk of invasive cancers, but less effective at reducing noninvasive cancers[c]	65% at 3 years[d]	53% at 5 years[e]
Important toxicities	Vasomotor symptoms, cataracts, vascular events (stroke, TIA, VTE), and endometrial cancer and uterine sarcoma in postmenopausal women	Vasomotor symptoms, cataracts, vascular events (25% lower risk of vascular events than with tamoxifen)	Vasomotor symptoms, vaginal dryness, sexual dysfunction, arthralgia, headaches, and insomnia	Vasomotor symptoms, vaginal dryness, sexual dysfunction, arthralgia, carpal tunnel syndrome, dry eyes, and hypertension
Indicated for use in premenopausal women	Yes	Not studied; should not be used unless part of a clinical trial	Not effective in premenopausal women	Not effective in premenopausal women
Other	Contraindicated in women with prior thromboembolic events; 32% reduction in osteoporotic fractures[a]	Contraindicated in women with prior thromboembolic events	At 3-year follow-up, no increase in osteoporosis, fractures, endometrial cancer, vascular events, or cardiac disease	At 5-year follow-up, no increase in thromboembolic events, fractures, cerebrovascular events, or myocardial infarction

SERM = selective estrogen receptor modulator; TIA = transient ischemic attack; VTE = venous thromboembolism.

[a]Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005 Nov 16;97(22):1652-62. [PMID: 16288118]

[b]Cuzick J, Sestak I, Cawthorn S, et al; IBIS-I Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015 Jan;16(1):67-75. [PMID: 25497694]

[c]Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006 Jun 21;295(23):2727-41. Erratum in: JAMA. 2006 Dec 27;296(24):2926. [PMID: 16754727]

[d]Goss PE, Ingle JN, Alés-Martínez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. [PMID: 21639806]

[e]Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014 Mar 22;383(9922):1041-48. Erratum in: Lancet. 2014 Mar 22;383(9922):1040. [PMID: 24333009]

TABLE 6. Staging and Prognosis of Invasive Breast Cancer

Stage	Definition	5-Year Relative Survival[a] Rates
0	Ductal carcinoma in situ (negative lymph nodes)	100%
Localized	IA: Tumor ≤2 cm and negative lymph nodes	98.9%
	IB: Tumor ≤2 cm and 1 to 3 micrometastatic positive lymph nodes (0.2-2 mm)	
Regional	IIA: Tumor ≤2 cm with 1 to 3 positive lymph nodes (>2 mm) *OR*	85.7%
	Tumor 2-5 cm with negative lymph nodes	
	IIB: Tumor 2-5 cm with 1 to 3 positive lymph nodes *OR*	
	Tumor >5 cm with negative lymph nodes	
	IIIA: Tumor ≤5 cm with 4 to 9 positive lymph nodes *OR*	
	Tumor >5 cm with 1 to 9 positive lymph nodes	
	IIIB: Tumors with skin or chest wall involvement with 0 to 9 positive lymph nodes	
	IIIC: Tumors with 10 or more positive lymph nodes	
Distant	Distant metastatic disease	28.1%

[a]Relative survival is the ratio of the proportion of observed survivors in a cohort of patients with cancer to the proportion of expected survivors in a comparable set of cancer-free individuals.

Data from Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020. Accessed January 1, 2021.

Breast cancer survival has improved dramatically. American Cancer Society data from 1989 to 2017 show a 40% decrease in deaths from breast cancer. The 5-year relative survival for all invasive breast cancer stages in patients diagnosed from 2010 to 2016 is 91.4%.

KEY POINTS

- Clinical features associated with a more favorable prognosis of early-stage breast cancer include hormone receptor–positive cancer, small tumor size, low tumor grade, negative lymph nodes, and the absence of *HER2* overexpression.

HVC

- Imaging studies such as PET, CT, or bone scan for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.

Primary Breast Cancer Therapy

Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), classified as stage 0 breast cancer, is a noninvasive breast cancer that usually presents as calcifications on mammography (**Figure 1**). Its incidence has increased greatly, from 3% of breast cancers before the era of mammographic screening to 20% to 25% of breast cancers today. Patients with DCIS infrequently present with a palpable mass or with Paget disease of the breast (see Invasive Breast Cancer).

Because half of local recurrences of DCIS are invasive cancers, the goal of treatment is to eradicate the area of DCIS and decrease the risks of local recurrence and deaths from breast cancer. Surgical treatment involves either lumpectomy, often followed by breast irradiation, or mastectomy. Irradiation may be omitted in some cases of estrogen receptor–positive DCIS. Mastectomy is recommended if the DCIS is more extensive and cannot be fully removed by a wide excision. Post-lumpectomy irradiation and mastectomy improve disease-free survival but not breast cancer–specific mortality.

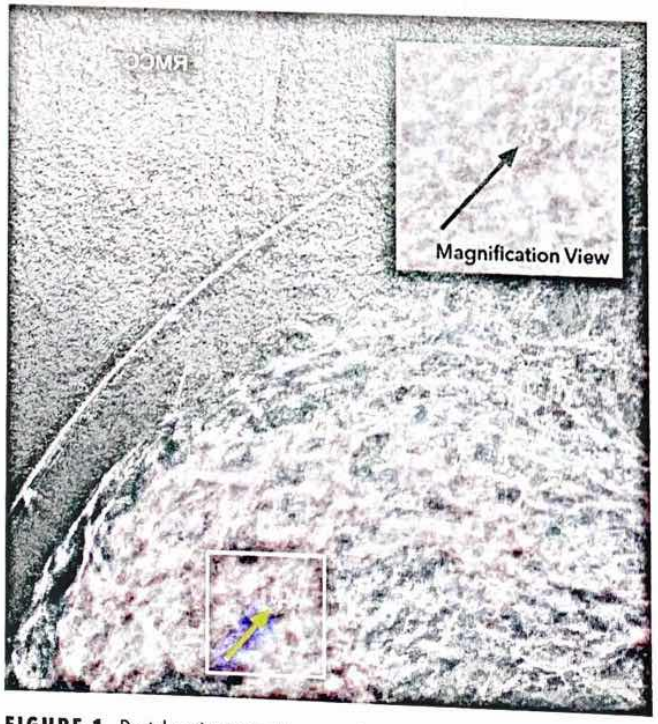

FIGURE 1. Ductal carcinoma in situ presenting as calcifications on mammography.

In women with estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors decrease the risks of local recurrence and contralateral breast cancers. Tamoxifen is the appropriate treatment in premenopausal women. For postmenopausal women, both tamoxifen and anastrozole are effective options; antiestrogen treatment of DCIS does not increase survival. Adjuvant endocrine therapy is not indicated.

Patients with DCIS should undergo annual mammography starting 6 to 12 months after radiation therapy, if given, and follow-up visits every 6 to 12 months for 5 years after diagnosis.

KEY POINTS

- Mastectomy or post-lumpectomy irradiation decreases the risk for local recurrence in women with ductal carcinoma in situ but does not improve overall 10-year survival.
- In estrogen receptor–positive ductal carcinoma in situ, tamoxifen and aromatase inhibitors further decrease the risks of local recurrence and contralateral breast cancer but do not improve overall survival.

Invasive Breast Cancer

Most early-stage invasive breast cancers are treated with initial excision followed by irradiation and adjuvant systemic therapy. There are two surgical options for invasive breast cancer. Breast conservation therapy involves wide excision followed by breast irradiation and is typically used in patients with cancers 5 cm or less in size, without skin involvement, and with clear margins after excision. Mastectomy is recommended for cancers that are too large to allow a lumpectomy with an acceptable cosmetic outcome, cancers with skin involvement, and inflammatory breast cancers. Mastectomy may also be chosen in situations when irradiation is contraindicated, or in women with *BRCA1* or *BRCA2* mutations or strong family histories of breast cancer in which there is a high risk of new breast cancers. For some patients with large tumors, neoadjuvant chemotherapy or endocrine therapy can be given before surgery to shrink the tumor to facilitate breast conservation.

A sentinel node biopsy is done at the time of breast surgery in patients with clinically negative axillary lymph nodes. In patients undergoing breast conservation surgery who will receive chemotherapy or antiestrogen therapy as well as whole breast irradiation, axillary dissection is not required if no more than two sentinel nodes are involved. For patients with clinically involved axillary nodes or three or more positive sentinel

nodes, an axillary dissection is recommended. An axillary dissection is also performed if the sentinel nodes are not identified, which occurs in 5% of cases. The sentinel node procedure has a lower risk of lymphedema, sensory loss, and shoulder abduction defects than axillary dissection.

Primary breast irradiation usually consists of irradiation to the whole breast, although partial breast irradiation is an option in some patients. Postmastectomy irradiation is generally recommended for tumors larger than 5 cm, positive margins or skin involvement, inflammatory breast cancers, or four or more positive axillary nodes and often for women with one to three positive axillary nodes. Postmastectomy irradiation decreases both the risk of local recurrence and the risk of distant metastases and increases overall survival.

For women older than age 70 years with cancers less than 2 cm in size, no clinically involved lymph nodes, and estrogen receptor-positive breast cancer, wide excision followed by antiestrogen therapy alone is an acceptable treatment option. Whole breast irradiation in this situation decreases the risk of local recurrence from 9% to 2% at 12 years but has no impact on the risk of distant metastases, breast cancer-specific survival, or overall survival.

Paget disease of the breast is an uncommon manifestation of breast cancer, characterized by a scaly or red rash or ulceration occurring on the nipple and spreading to the areola. It may have a similar appearance to atopic or contact dermatitis. Paget disease usually occurs in association with an underlying ductal breast cancer and is diagnosed through a skin biopsy or scrape cytology, which shows involvement of the epidermis by neoplastic cells. Upon diagnosis, patients should undergo diagnostic breast imaging and, if no abnormalities are detected, breast MRI should be considered to evaluate for occult disease. Prognosis and management are determined by the standard features of an in situ or invasive carcinoma. Depending on the extent of disease within the breast, breast-conserving therapy may be appropriate, although all patients require nipple-areolar resection.

KEY POINTS

- Breast-conserving therapy is effective for many women with small (<5 cm) tumors, no skin involvement, and clear margins after resection; breast irradiation is recommended subsequently in most patients.
- Postmastectomy irradiation is recommended for cancers greater than 5 cm in size, positive margins or skin involvement, inflammatory breast cancers, and most patients with positive axillary lymph nodes.

Adjuvant Systemic Therapy for Nonmetastatic Breast Cancer

Patients with stage I to III (potentially curable) breast cancer receive adjuvant systemic therapy to eradicate occult microscopic foci of breast cancer and decrease the risk of local and distant recurrence. The type of adjuvant therapy used depends on the biology and stage of the breast cancer.

Adjuvant Endocrine Therapy

Approximately 75% of breast cancers are hormone receptor-positive (positive for the estrogen receptor, progesterone receptor, or both). Patients with hormone receptor-positive breast cancers should receive adjuvant antiestrogen therapy for at least 5 years. The Early Breast Cancer Trialists Collaborative Group meta-analysis of adjuvant tamoxifen showed a 39% proportional reduction in breast cancer recurrence at 15 years and a 30% proportional reduction in breast cancer mortality. In postmenopausal women, aromatase inhibitors are superior to tamoxifen, with a further 29% proportional decrease in breast cancer recurrence. Both tamoxifen and aromatase inhibitors also decrease the risk of contralateral breast cancer.

Tamoxifen is a selective estrogen receptor modulator that blocks estrogen uptake by breast cancer cells. It is effective in both premenopausal and postmenopausal women. The aromatase inhibitors letrozole, anastrozole, and exemestane have similar efficacy and prevent conversion of adrenal androgens to estrogen but do not inhibit ovarian estrogen production. They are thus not effective in premenopausal women unless ovarian suppression is given concomitantly.

For postmenopausal women, 5 years of an aromatase inhibitor or 2 years of tamoxifen followed by 3 years of an aromatase inhibitor is associated with a significantly lower risk of recurrence and with improved survival in women with higher-grade ductal cancers or lobular cancers. Extended aromatase therapy up to 10 years reduces disease-free survival in patients with high-risk features but does not have an impact on overall survival. Decisions regarding extended aromatase inhibitor therapy should be tailored to patient risk and comorbidities that may affect tolerability, including bone health and history of venous thromboembolic disease.

Endocrine therapy options for premenopausal women with estrogen receptor-positive breast cancer include tamoxifen, ovarian function suppression (OFS) with tamoxifen, or OFS with an aromatase inhibitor. For those with low recurrence risk, tamoxifen alone for 5 years may be appropriate. Extended tamoxifen therapy to 10 years is associated with a reduction in recurrence risk (3.7%) and breast cancer mortality (2.8%). Disease-free survival is improved in premenopausal women with higher-risk cancers with the addition of OFS. Patients treated with OFS had more hot flushes, vaginal dryness, decreased libido, insomnia, depression, arthralgia, hypertension, glucose intolerance, and osteoporosis.

Adverse effects of tamoxifen and aromatase inhibitors are shown in Table 5. Up to one third of women treated with aromatase inhibitors develop aromatase inhibitor-associated symmetric arthralgia, joint stiffness, and bone pain. This musculoskeletal syndrome is managed with NSAIDs or duloxetine, a treatment break and changing to an alternate aromatase inhibitor, or a change to tamoxifen.

KEY POINTS

- Endocrine therapy in women with hormone receptor–positive breast cancer substantially reduces the risk of recurrence and improves overall survival.
- Endocrine therapy options for premenopausal women include tamoxifen, ovarian function suppression (OFS) plus tamoxifen, or OFS plus an aromatase inhibitor; women at low recurrence risk may be treated with tamoxifen alone.
- Five years of an aromatase inhibitor or 2 years of tamoxifen followed by 3 years of an aromatase inhibitor is associated with a significantly lower risk of recurrence and with improved survival in postmenopausal women with higher-grade ductal cancers or lobular cancers.
- Extended aromatase inhibitor treatment up to 10 years reduces recurrence risk relative to 5 years in patients with higher-risk cancer but does not improve overall survival.

Adjuvant Chemotherapy

Increasingly, the use of adjuvant chemotherapy for early breast cancer is based more on tumor biology rather than on stage. Hormone receptor–negative and *HER2*-positive cancers are associated with greater recurrence as well as greater risk reduction from chemotherapy. Adjuvant chemotherapy is recommended for women with cancers of these subtypes that are either greater than 5 mm or lymph node positive.

For hormone receptor–positive, *HER2*-negative breast cancers with zero to three positive axillary nodes, the use of multigene assays (e.g., the 21-gene recurrence score assay) that predict the risk of recurrence with antiestrogen therapy alone has significantly decreased the use of adjuvant chemotherapy. Women with node-negative breast cancer and low and intermediate recurrence scores have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy. Similar findings have been seen for women with one to three positive nodes with low and intermediate risk recurrence scores, but these conclusions remain controversial.

Clinicopathologic factors that suggest benefit from adjuvant chemotherapy include high tumor grade, extensive lymphatic invasion, larger tumor size, skin or chest wall involvement, and involvement of more than four axillary nodes.

Women with hormone receptor–negative, *HER2*-negative cancers (triple-negative breast cancer) have a 50% proportional reduction in the risk of recurrence and of breast cancer mortality with adjuvant chemotherapy. Adjuvant chemotherapy is recommended for patients with triple-negative cancers larger than 5 mm in size or with positive lymph nodes.

When adjuvant chemotherapy is given for high-risk hormone receptor–positive cancers or triple-negative cancers, typically two or three agents are given for four to eight cycles. The most common chemotherapies used for adjuvant treatment are anthracyclines (doxorubicin or epirubicin), cyclophosphamide, and the taxanes (paclitaxel or docetaxel).

Adjuvant chemotherapy combined with *HER2*-targeted treatment such as the monoclonal antibody trastuzumab or the combination of trastuzumab and pertuzumab is recommended for *HER2*-positive cancers that are greater than 5 mm in size, node positive, or both. The addition of trastuzumab to chemotherapy decreases the risk of cancer recurrence by 53% and the risk of death by 34%. Trastuzumab is generally given for 12 months in total. For patients with node-negative *HER2*-positive breast cancers smaller than 3 cm in size, weekly paclitaxel and trastuzumab is a well-tolerated regimen with a 7-year recurrence-free survival rate of 97.5%. Neoadjuvant chemotherapy is generally recommended for patients with larger or node-positive tumors and involves multiple chemotherapy agents along with trastuzumab and pertuzumab. Patients with no residual disease at surgery have an excellent prognosis. Patients with residual disease following preoperative chemotherapy have a greater recurrence risk, and subsequent use of ado-trastuzumab-emtansine (an antibody-drug conjugate that links trastuzumab to the microtubule inhibitor emtansine) reduces recurrence risk by 50% relative to trastuzumab. The main toxicities of trastuzumab are infusion reactions such as fever, chills, and cardiomyopathy.

Acute adverse effects of adjuvant chemotherapy include bone marrow suppression, alopecia, allergic reactions, neuropathy, nausea, and premature menopause and infertility in premenopausal women (see Effects of Cancer Therapy and Survivorship). Women of childbearing age who wish to preserve fertility may undergo oocyte or embryo banking before chemotherapy. Serious long-term toxicities include cardiomyopathy, neuropathy, myelodysplasia, and acute myelocytic leukemia. The risk of cardiomyopathy after four cycles of an anthracycline is 1.5%. The risk of acute leukemia after regimens containing an anthracycline or cyclophosphamide is 0.5%.

For women of advanced age with higher-risk early breast cancer, it is important to consider estimated life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy. There is a higher risk of cardiotoxicity in older women.

KEY POINTS

- Patients with hormone receptor–positive, node-negative breast cancer and low or intermediate risk recurrence scores have a favorable prognosis with antiestrogen therapy and do not benefit from chemotherapy.
- Adjuvant chemotherapy is appropriate for patients with triple-negative or *HER2*-positive tumors greater than 5 mm in size or with positive axillary lymph nodes.

Locally Advanced and Inflammatory Breast Cancer

Locally advanced breast cancer includes a subset of clinical stage IIB cancers (T3N0M0), as well as stages IIIA to IIIC cancers. These cancers may have high-risk characteristics such as skin involvement, chest wall involvement, extensive lymph node involvement, or inflammatory changes.

Inflammatory breast cancer represents a small subset of locally advanced breast cancer in which patients present with swelling, thickening, or erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance (**Figure 2**). Patients often present with breast enlargement or swelling, often misdiagnosed as mastitis with subsequent delay in management. A palpable breast mass may be present. The skin changes are due to the obstruction of dermal lymphatic vessels by cancer cells, although biopsy may not always reveal that pathology. One third of patients have distant metastases at diagnosis, and nearly all have lymph node involvement. For this reason, these patients should have routine staging with either CT and bone scan imaging or PET scan, even in the absence of metastatic disease symptoms.

Locally advanced cancers are usually treated initially with neoadjuvant chemotherapy, followed by surgery, and then irradiation. In some postmenopausal women, neoadjuvant antiestrogen therapy can be used instead of chemotherapy. Patients with inflammatory breast cancer require mastectomy, but in other patients, neoadjuvant therapy may decrease the size of the primary breast cancer to allow for breast-conserving lumpectomy. Patients will generally receive radiation therapy afterward. The amount of residual cancer after neoadjuvant chemotherapy has prognostic significance, particularly in triple-negative or hormone-negative, *HER2*-positive cancers. Patients with complete pathologic responses have the lowest risk of recurrence, whereas those with residual disease may benefit from treatment intensification with additional chemotherapy.

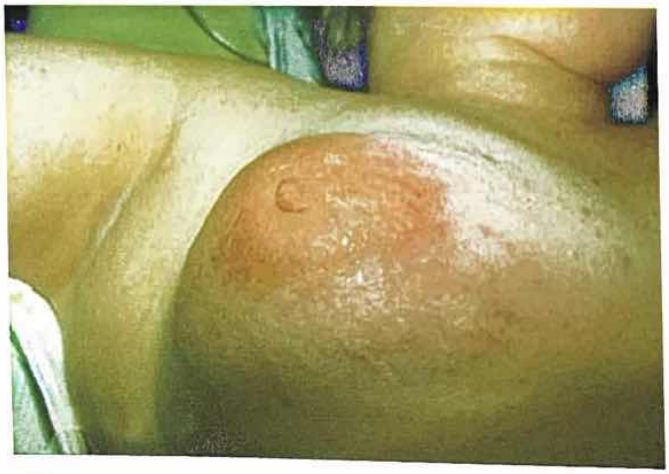

FIGURE 2. Inflammatory breast cancer often has a characteristic "p'eau d'orange" (orange peel) appearance of the skin, due to tumor emboli in the dermal lymphatics. Erythema is also often present.

KEY POINTS

- Inflammatory breast cancer, characterized by swelling, thickening, and erythema of the skin overlying the breast, may be mistaken for infectious mastitis and delay evaluation and treatment.
- Locally advanced cancers are usually treated with neoadjuvant chemotherapy or endocrine therapy, surgery, and irradiation.

Breast Cancer Follow-up and Survivorship

There are nearly 3 million women alive in the United States with a previous or current diagnosis of breast cancer. Following early active therapy (surgery, chemotherapy, and irradiation), patients are monitored for recurrence, second primary cancers, and physical and psychosocial long-term effects of breast cancer and treatment. Patients with hormone receptor-positive breast cancer remain on antiestrogen treatment for 5 to 10 years and require management of menopausal symptoms and other toxicities, including bone loss, during that time. Guidelines recommend that patients be evaluated for a detailed cancer-related history and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually.

Patients should have annual mammograms of remaining breast tissue. Screening breast MRIs are needed only if patients meet criteria for screening MRIs (see Chemoprevention and other Risk Reduction Strategies). Patients should not have routine blood tests at follow-up visits or other routine imaging studies, as these are not helpful for diagnosing recurrences earlier. Laboratory and imaging studies other than breast imaging should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.

Patients should be evaluated at each visit for changes in family history of cancers and referred for genetic counseling as appropriate. Patients on tamoxifen should have annual gynecologic examinations and be evaluated by a gynecologist for any abnormal vaginal bleeding. Patients on aromatase inhibitors should have bone density studies every 2 years and should receive osteoporosis treatment, ideally with a bisphosphonate, if their T score is -2.5 or lower.

For patients with breast asymmetry, reconstruction options are often fully covered by insurance. Patients should receive physical therapy for lymphedema or decreased arm mobility after surgery or irradiation to axillary nodes. Menopausal symptoms should be managed with nonhormonal options, such as gabapentin for nocturnal hot flushes. Depression, anxiety, and sexual dysfunction are not uncommon in this population and should be appropriately assessed and managed. For patients taking tamoxifen, it is important to avoid medications with strong CYP2D6 inhibition, such as bupropion or fluoxetine, as these may decrease tamoxifen activation.

KEY POINTS

- After completing treatment for breast cancer, follow-up monitoring should be every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then every year, with annual mammography for all survivors, and breast MRI for those at high risk of recurrence.
- Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.
- Patients taking tamoxifen should have yearly gynecologic examinations because of the increased risk of endometrial cancer, and those on an aromatase inhibitor should have bone density studies every other year to assess osteoporosis.

Metastatic Breast Cancer

Approximately 5% of patients with breast cancer present with metastatic disease, and up to 30% with early-stage disease develop metastases. Metastatic breast cancer is not curable, but systemic therapy can improve survival, relieve symptoms, and maintain quality of life. Treatment and prognosis are related to whether visceral metastases are present, the number of sites involved, the interval between initial diagnosis and metastases (intervals of less than 2 years have a poorer prognosis), the patient's performance status, and tumor biology. The median overall survival for patients with metastatic breast cancer is longer for women with hormone receptor–positive cancer or *HER2*-positive cancer, some of whom may have prolonged survival, in part related to more treatment options.

When evaluating a patient with newly diagnosed metastatic breast cancer, the lesion that upstages the patient to the greatest degree should be biopsied. It is also important to biopsy a site of initial metastasis both to confirm the diagnosis and to assess hormone receptor and *HER2* status, as there may be treatment altering discordance in the receptors in the metastatic lesion compared with the primary breast cancer in 10% to 15% of patients.

In postmenopausal women with hormone receptor–positive, *HER2*-negative breast cancer, endocrine-based therapy is usually the initial treatment. In patients with rapidly progressive disease or extensive visceral metastases, initial chemotherapy may be used because of its higher response rate. Aromatase inhibitors are superior to other agents as first-line treatment. Fulvestrant, which inhibits estrogen receptor function, and tamoxifen are other options. Premenopausal women can receive tamoxifen or ovarian suppression combined with either tamoxifen or aromatase inhibitors as initial treatment.

The addition of CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) to aromatase inhibitors as first-line endocrine therapy or to fulvestrant following progression on an aromatase inhibitor improves the response rate and duration of response to hormonal therapy. These drugs have been incorporated into routine care for the majority of women with metastatic estrogen receptor–positive/*HER2*-negative breast cancer.

For patients with *HER2*-positive advanced breast cancer, treatment should include *HER2*-directed therapy such as trastuzumab given with either chemotherapy or antiestrogen therapy, depending on the hormone receptor status of the cancer and disease sites. First-line treatment with dual *HER2*-targeted therapy with trastuzumab and pertuzumab added to the taxane docetaxel has been shown to improve overall survival, with median overall survival of 56 months in a phase III clinical trial. Ado-trastuzumab emtansine is commonly used as a second-line treatment but may be used as first-line therapy following a treatment-free interval of less than 6 months from adjuvant trastuzumab.

Patients with triple-negative breast cancers (TNBC have a higher relapse rate than individuals with hormone receptor–positive cancers; recur earlier, with a peak at 3 years after diagnosis and a very low risk of relapse after 5 years; and have a higher risk of locoregional recurrence and brain and lung metastases. Advanced TNBC has historically been treated with chemotherapy. The addition of atezolizumab, a monoclonal antibody targeting programmed death ligand 1, to nab-paclitaxel improved overall survival (23.1 vs 17.6 months) for patients with programmed death ligand 1–positive metastatic TNBC. TNBC may also be particularly responsive to platinum agents, particularly in *BRCA* mutation carriers. In patients with germline *BRCA1* or *BRCA2* mutations, poly (ADP-ribose) polymerase inhibitors (olaparib, talazoparib) improve progression-free survival relative to single-agent chemotherapy. These agents cause "synthetic lethality" by producing an increase in double-strand DNA breaks that would usually be repaired by the *BRCA* pathway.

Chemotherapy agents used in patients with advanced breast cancer include taxanes, capecitabine, eribulin, gemcitabine, vinorelbine, ixabepilone, and liposomal doxorubicin. Single-agent chemotherapy is usually given, with combination chemotherapy reserved for patients with extensive visceral metastases where a higher response rate is important.

For all subtypes of breast cancer with bone metastases, bone-modifying agents such as zoledronic acid or denosumab are recommended to decrease fractures, pain, and need for irradiation. Palliative irradiation can be used to treat painful bone metastases as well as other sites of tumor-related pain or obstruction. Patients with TNBC and *HER2*-positive cancers have a higher risk of brain metastases, which are treated with surgery, stereotactic irradiation, or whole brain irradiation. Palliative care teams can be helpful for managing symptoms of pain, nausea, anorexia, and fatigue. Throughout the course of advanced breast cancer, discussions with patients about their goals of care should

take place, focusing on their values and preferences as they are treated for an incurable illness.

KEY POINTS

- Metastatic breast cancer is not curable, but it can be treated with systemic therapy with the goals of improved survival, symptom palliation, and maintaining quality of life.
- The site of initial metastasis should be biopsied to confirm the diagnosis and to assess hormone receptor and *HER2* status, which can be discordant from the primary breast cancer.

Ovarian Cancer

Epidemiology and Risk Factors

Risk factors for epithelial ovarian cancer include mutations of ovarian cancer susceptibility genes, increasing age, infertility, nulliparity, endometriosis, polycystic ovary syndrome, and cigarette smoking.

The most common ovarian cancer susceptibility genes are *BRCA1*, *BRCA2*, and the mismatch repair (MMR) genes associated with Lynch syndrome. Approximately 10% to 15% of women with ovarian cancer carry a mutation in one of these genes, and all women with epithelial ovarian cancer should be offered germline genetic testing for *BRCA1* and *BRCA2* mutations. In patients with a personal or family history of other Lynch syndrome cancers (e.g., colorectal cancer, cancer of the endometrium or small bowel, transitional cell carcinoma of the ureter or renal pelvis), MMR mutation testing is recommended as well. The cumulative lifetime risk of ovarian cancer is 45% in *BRCA1* carriers and 3% to 12% in the other gene mutation carriers.

KEY POINT

- Genetic testing for *BRCA1* and *BRCA2* mutations should be offered to all women with ovarian cancer.

Risk-Reduction Strategies and Screening

For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing. For *BRCA1* or *BRCA2* carriers, prophylactic bilateral salpingo-oophorectomy decreases the risk of ovarian cancers by greater than 80% and decreases all-cause mortality to age 70 years by 77%. Recommendations for genetic testing for breast and ovarian cancer syndromes are discussed in Breast Cancer.

Ovarian cancer screening with transvaginal ultrasonography or serum CA-125 is not recommended for patients of average risk and has no proven benefit even in women with high-risk genetic mutations.

KEY POINT

- For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing.

Diagnosis

Patients with ovarian cancer usually present at an advanced stage with bloating, abdominal or pelvic pain, constipation, or early satiety. Initial evaluation should include a pelvic examination, general physical examination, serum CA-125 level, complete blood count, liver chemistry tests, and transvaginal ultrasonography. Additional CT or MRI imaging are done as clinically indicated. Patients with a high suspicion of ovarian cancer should be referred to a gynecologic oncologist.

For early ovarian cancer, surgical exploration is recommended for diagnosis because removing the ovarian cancer intact without rupture improves survival. For advanced ovarian cancers with peritoneal masses, ascites, or pleural effusions, fluid cytology or image-guided biopsy can be done, particularly if the disease is not initially resectable and neoadjuvant chemotherapy may be used.

Staging and prognosis are shown in **Table 7**. Early stage, low grade, serous histology, extent of disease after surgical debulking, and young age are associated with improved survival. A total of 31% of patients diagnosed with ovarian cancer survive 10 years, with one third of these long-term survivors having stage III or IV cancer.

Treatment

Surgical staging includes total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings, omentectomy, and pelvic and para-aortic lymph node sampling. Surgical debulking, including the resection of metastatic disease, improves prognosis. The volume of residual disease after surgery correlates inversely with survival. Neoadjuvant chemotherapy is recommended for patients with initially unresectable disease to shrink the tumor to facilitate surgical debulking.

Patients with early-stage ovarian cancer who have favorable histology may be treated with surgical resection alone. All other patients should receive adjuvant platinum-taxane chemotherapy. When incorporated into systemic therapy, intraperitoneal chemotherapy has been shown to improve survival in some trials, albeit with more toxicity, in women with stage III disease.

Women with advanced ovarian cancer and *BRCA1* or *BRCA2* mutations who achieve some response to traditional chemotherapy should receive subsequent maintenance therapy with olaparib, a poly (ADP-ribose) polymerase inhibitor.

Second-look laparotomy to assess pathologic response is not beneficial.