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TABLE 83-14 Staging Thymic Tumors MASAOKA STAGE DEFINITION I Grossly and microscopically encapsulated IIA Microscopic transcapsular invasion IIB Macroscopic invasion into surrounding tissue excluding pericardium, lung, and great vessels III Macroscopic invasion into neighboring organs of the lower neck or upper chest IVA Pleural or pericardial dissemination IVB Hematogenous or lymphatic dissemination to distal organs WHO A Tumor with few lymphocytes AB Tumor with features of type A and foci rich in lymphocytes B1 Tumor with features of normal epithelial cells with vesicular nuclei and distinct nucleoli and an abundant population of lymphocytes. Also known as cortical thymoma, lymphocyte-rich thymoma B2 Thymoma with no or mild atypia with round or polygonalshaped cells with small component of lymphocytes B3 Well-differentiated thymic carcinoma with mild atypia C Thymic carcinoma with high atypia PART 4 Oncology and Hematology determine if the mass is resectable based on relationship to surround ing structures. An MRI with contrast may be performed if clinically indicated. A PET scan may be useful in the evaluation of a patient with thymic tumors, although it may be less useful in the staging of thymoma compared to thymic carcinoma. A core needle biopsy is considered standard of care for obtaining a histologic diagnosis of an anterior mediastinal tumor. This may be obtained via CT or ultrasound imaging. However, in some circumstances, a mediastinoscopy or open biopsy may be required. Thymomas are commonly staged using the Masaoka system or the WHO staging system, as described in Table 83-14. WHO types A, AB, and B1 tend to be more well-differentiated, types B2 and B3 are mod erately differentiated, and type C is poorly differentiated. ■ ■TREATMENT Surgical resection is the mainstay of treatment for patients with Masa oka type I and II thymic tumors. In patients with type III and IV who have potentially resectable thymic tumors, neoadjuvant chemotherapy may be given to decrease the tumor size and allow for a resection with negative margins. Surgery remains controversial and provides a limited role in the treatment of stage III and IV disease. No additional therapy may be required in patients with type I who have a resection with nega tive margins. Postoperative radiation therapy may be recommended based on extracapsular extension and the presence of positive margins in patients with type II or III thymic tumors or histologic evaluation WHO B3 and C. Radiation therapy may be beneficial in patients with locally advanced disease (type III or IV) or in patients with symptoms secondary to compression of surrounding structures. Chemotherapy with cisplatin, doxorubicin, and cyclophosphamide (CAP) remains the mainstay of therapy in the neoadjuvant and adjuvant setting as well as first-line therapy in patients with metastatic thymoma, whereas carboplatin and paclitaxel are often employed in patients with thymic carcinoma. Limited additional agents are recommended based on small phase 2 trials as second-line therapy and beyond. SUMMARY The management of SCLC and NSCLC has undergone major change in the past decade, resulting in a reduction in lung cancer mortality. For patients with early-stage disease, advances in radiotherapy and surgical procedures as well as new systemic therapies in the neoadjuvant and perioperative settings have greatly improved prognosis in all

diseases. For patients with advanced lung cancer, major progress in understand ing tumor genetics and tumor immunology has led to the development of rational targets and specific inhibitors, which have documented

efficacy in specific subsets of NSCLC. Furthermore, increased under standing of how to activate the immune system to drive antitumor immunity has proven to be a successful therapeutic strategy for a subset of patients with advanced lung cancer. However, only a small subset of patients responds to immune checkpoint inhibitors, and the majority of patients treated with targeted therapies or chemotherapy eventually develop resistance, which provides strong motivation for further research and enrollment of patients onto clinical trials in this rapidly evolving area. Acknowledgment David Johnson, Leora Horn, and Wade Iams contributed to this chapter in the prior edition and material from that chapter has been retained here. ■ ■FURTHER READING Cascone T et al: Perioperative nivolumab in resectable lung cancer. N Engl J Med 390:1756, 2024. Ettinger D et al: NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 2.2023. J Natl Compr Canc Netw 21:340, 2023. Hsu M et al: Lung cancer survivorship: Physical, social, emotional, and medical needs of NSCLC survivors. J Natl Compr Canc Netw 22:e237072, 2024. Owen D et al: Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO Living Guideline, Version 2023.2. J Clin Oncol 41:e63, 2023. Rudin C et al: Small-cell lung cancer. Nature Rev Dis Primers 7:3, 2021. Wakelee H: Chemotherapy and immunotherapy in early-stage NSCLC: Neoadjuvant vs adjuvant therapy. Clin Adv Hematol Oncol 21:648, 2023. Nancy E. Davidson

Breast Cancer Breast cancer is the most common nonskin cancer diagnosed in women in the world. In 2024, it is estimated that in the United States 310,000 women will be diagnosed with invasive breast cancer, >56,000 women will receive a diagnosis of ductal carcinoma in situ (DCIS), and about 42,250 women will die from breast cancer. Although largely a disease of women, about 2800 men will be diagnosed with and 530 men will die from breast cancer in 2024 in the United States. Thanks to advances in understanding of breast cancer biology, screening, diag nosis, treatment, and decreased use of hormone replacement therapy, 5-year relative survival in the United States is currently 91%. These advances have also made it possible to conceptualize the evolution of breast cancer and how available interventions can be applied across the continuum of changes to improve outcomes (Fig. 84-1). EPIDEMIOLOGY AND RISK FACTORS ■ ■NONGENETIC RISK FACTORS Female gender and increasing age are the most common risk factors for breast cancer. About 70% of breast cancer in the United States is diag nosed in women 55 years and older, and median age of diagnosis is 63. Incidence is highest in non-Hispanic whites followed by non-Hispanic blacks and is lower in Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native women; in contrast, mortality is highest in nonHispanic blacks followed by non-Hispanic whites and individuals of other race/ethnicity. Both incidence and mortality vary considerable around the globe, but studies of immigrant populations show that pop ulations who migrate from low-incidence regions to high-incidence regions will attain the breast cancer risk of the higher incidence region within one or two generations.

Breast cancer continuum High risk In situ Invasive Micro-metastases Detectable metastases Mortality Normal Ductal carcinoma in situ Normal duct Intraductal hyperplasia Atypical ductal hyperplasia Risk assessment Risk reduction/chemoprevention Screening Primary Rx (surgery/radiation) FIGURE 84-1 Breast cancer continuum conceptual model. Most breast cancers begin in epithelial cells within the lobules or ducts. They proceed through a continuum of atypia

and hyperplasia to in situ malignancy to invasion into surrounding normal tissues followed by intravasation into lymph and blood channels to local lymph nodes and distant organs, culminating in distant metastases. This is a conceptual model. Not all metastatic breast cancers have progressed through these stages, and many lesions do not progress to the next. Breast cancer is predominantly a disease resulting from prolonged exposure of the breast to estrogen. Thus, early menarche, late meno pause, and late first pregnancy are known risk factors. Likewise, pro longed exposure to hormone replacement therapy (but paradoxically not estrogen replacement therapy) is associated with increased risk as is current use of oral contraceptives. Postmenopausal obesity (but not premenopausal obesity) is also a risk factor, likely because of increased estrogen exposure. Studies of diet and breast cancer risk have not been conclusive, but alcohol consumption is a risk factor. The best documented exogenous risk factor for breast cancer is exposure to ionizing radiation during adolescence. Studies of other environmental factors such as pesticide or other chemical exposures have not been convincing. Women diagnosed with some types of benign breast pathology also have a higher risk of subsequent invasive breast cancer diagnosis. In particular, the diagnosis of atypical ductal or lobular hyperplasia increases risk about four- to fivefold, whereas a diagnosis of lobular carcinoma in situ (LCIS) increases risk 7- to 12-fold. Recent studies also suggest that women with high breast density on mammography may be at increased risk of breast cancer. ■ ■GENETIC RISK FACTORS Family history is a critical risk factor, although only 20% of women diagnosed with breast cancer have a family history. Diag nosis of breast cancer in a first-degree relative (parent, sibling, or daughter) doubles breast cancer risk. A personal diagnosis of previous invasive breast cancer also increases the risk of developing a new breast cancer in the ipsilateral or contralateral breast. Prevention, diagnosis, and management of breast cancer have been revolutionized by the identification of a family of hereditary breast cancer susceptibility genes that account for 5–10% of breast cancers. These genes play a role in DNA damage repair, and inherited muta tions, which are transmitted in an autosomal dominant fashion,

Regional lymph node Lymph or blood vessels Invasive ductal cancer Distant organs Distant organs CHAPTER 84 Adjuvant Systemic Rx Breast Cancer Survivorship Palliative treatment generally lead to protein truncation and loss of function of DNA repair proteins. The most common mutations are in the BRCA1 (located on chromosome 17q21) or BRCA2 (located on chromosome 13q12) genes, and they impart a 50–80% risk of developing invasive breast cancer by age 80 years as well as a 30% risk of developing ovarian cancer. Germline mutations in other genes also lead to a higher risk of breast cancer including TP53 (Li-Fraumeni syndrome), PALB2, ATM, STK11 (Peutz-Jeghers syndrome), and PTEN (Cowden syndrome). Certain populations have a higher incidence of BRCA mutations, especially Ashkenazi Jews. Commercially available assays for germline, breast cancer susceptibility mutations have expanded from just the two originally discovered genes (BRCA1/2) to panels including these and the genes listed above to panels that include these and 20 or more additional genes. Two major concerns have arisen over time regarding the relative lack of clinical correlations inherent in these panels and the unknown association with risk, which have led to some confusion and discomfort among patients: (1) variants of unknown significance (VUS) in the genes known to be associated with increased risk; and (2) genes included in the panels about which little is known regarding clinical risk. Efforts to develop polygenic risk scores that evaluate single nucleotide polymorphisms (SNPs) in other genes are under study but are not yet ready for clinical application. Testing for germline mutations is readily done using panel testing on DNA obtained from peripheral blood or saliva after appropriate coun seling. It is not recommended for the general population. Evidencebased guidelines from the American Society of Clinical Oncology

and Society of Surgical Oncology recommend consideration of testing for high-penetrance breast cancer susceptibility genes in individuals with a personal history of breast cancer with specific features including diagnosis ≤65 years. Older patients should be offered testing for clini cal features such as Ashkenazi Jewish ancestry; multiple breast cancers; certain types of breast cancer, including breast cancer lacking expres sion of the estrogen and progesterone receptors and HER2 proteins

(triple-negative breast cancer [TNBC]) and lobular breast cancer with personal or family history of diffuse gastric cancer; or close blood rela tive with early-onset or male breast cancer, ovarian cancer, pancreatic cancer, or metastatic prostate cancer. Testing for individuals without a cancer diagnosis should be considered for those with a family member who tests positive or those with a family history as outlined above or those with higher risk based on existing risk assessment tools such as Tyrer-Cuzick score, BRCAPro, or CanRisk.

PREVENTION Current strategies to prevent breast cancer include surgery, chemo prevention, and lifestyle modification; their use and impact will vary depending on the underlying risk of developing breast cancer. ■ ■PROPHYLACTIC SURGERY Prophylactic mastectomy reduces risk of developing breast cancer by about 90% including in individuals who carry a germline breast cancer susceptibility gene mutation. Women who opt for prophylactic mastectomy in this setting should be counseled that breast cancer may develop in residual breast tissue. However, preventive mastectomy is not likely to improve outcomes in women with low or only modest risk and should be discouraged. Though the primary role for prophylactic oophorectomy is for ovarian cancer prevention in germline mutation carriers, it can also reduce breast cancer incidence in premenopausal women by about 50% because of reduction in estrogen exposure. PART 4 Oncology and Hematology ■ ■CHEMOPREVENTION Ample evidence exists for the use of chemoprevention approaches that target estrogen signaling pathways in high-risk women. Tamoxifen reduces risk of invasive breast cancer in women at higher risk (≥60 years, diagnosis of LCIS, or younger women with risk of developing invasive breast cancer ≥1.67% over 5 years based on current risk assessment tools). Newer data suggest that low-dose tamoxifen for 3 years may be effective and well tolerated. Side effects include postmenopausal symp toms and increased risk for endometrial cancer and thromboembolic events, especially in women over 50. Raloxifene may be an alternative for postmenopausal women. Though less effective in reducing breast cancer risk than tamoxifen, it is associated with fewer uterine cancers. The aromatase inhibitors, exemestane or anastrozole, also reduce breast cancer incidence by about 50% in postmenopausal women who are at moderate-high risk for breast cancer. The U.S. Preventive Services Task Force recommends that clinicians offer risk-reducing medications like tamoxifen, raloxifene, or aromatase inhibitors to women who are at increased risk for breast cancer and at low risk for medication side effects. Uptake is low despite the substantial evidence that demonstrates a huge benefit. ■ ■LIFESTYLE MODIFICATION Potential lifestyle modifications to reduce breast cancer risk include maintenance of a normal body mass index, avoidance of alcohol, and minimizing use of hormone replacement therapy. Regular exercise, especially during adolescence, may be associated with reduced risk. Long-term follow-up from the dietary substudy of the Women’s Health Initiative showed that a low-fat diet in postmenopausal women who were cancer-free at the time of study enrollment resulted in a nonsig nificant reduction in breast cancer incidence but appeared to reduce risk of death from breast cancer. The role of newer GLP-1 agents has not been studied. SCREENING Breast cancer screening has been an area of active investigation and controversy for decades. Issues include lack

of consensus around the goal of screening, the target population (e.g., age, risk), and the type and frequency of screening. Multiple guidelines exist and continue to evolve. Initial trials focused on three modalities: breast self-exam, clini cal breast exam (CBE), and mammography. Though widely promoted in the past, emphasis on breast self-exam has waned, in part because of two randomized clinical trials in China and Russia that showed no benefit. In contrast, a randomized trial in India of CBE every 2 years in

women aged 35–64 years with no history of breast cancer indicated that CBE led to a significant reduction in the proportion of women diag nosed with stage III or IV disease and a nonsignificant 15% reduction in breast cancer mortality, largely in women ≥50 years. Nine randomized trials have studied screening mammography. In aggregate, they demonstrated that screening mammography reduced breast cancer mortality by about 20–25% in women ≥50 years without an impact on overall mortality. The UK Age trial suggested a simi lar benefit for women who began screening at 40 years. Screening frequency has varied from 1–2 years across trials. Mammography techniques have evolved over the years, and a current U.S. trial is evaluating the role of tomosynthesis as a means of improving ben efit from mammography. Multiple guidelines exist and continue to evolve. Most recommend that women aged 50–70 years have mam mography every 1–3 years, and many recommend screening for women aged 40–50 years as well. When to stop is not known, but it is generally accepted that benefits are limited to women with a predicted life expectancy of at least 10 years. The role of magnetic resonance imaging (MRI) as a screening modality is less well studied. MRI is more sensitive, less specific, and more complex to perform. Some guidelines suggest that it be used for women who have a lifetime predicted risk of ≥20%, which includes those with germline pathogenic mutations in the BRCA genes. Its use has also been suggested for those with very dense breasts on mam mography, but clear evidence of benefit is lacking. Screening ultra sound has also been studied, but evidence supporting its routine use is lacking. There is considerable interest in the use of multicancer early detec tion (MCED) tests using circulating DNA as a screening test for dis eases like breast cancer. Initial studies have not shown that these tests can substitute for or augment conventional mammographic screening, and women who do have MCED assays performed should still undergo mammographic screening, even if the MCED test is negative. DIAGNOSIS AND STAGING Clinical signs and symptoms suggestive of breast cancer may include a breast lump or skin or nipple changes or palpable regional nodes. Thanks to mammographic screening, many patients present with abnormal mammographic findings including a mass, distortion, and/ or suspicious microcalcifications without any symptoms or physi cal exam findings. Figure 84-2 shows an algorithm for diagnostic evaluation of breast abnormalities noted on physical exam or imaging. Final diagnosis rests on pathologic confirmation, which is generally carried out by image-guided core biopsy to confirm diagnosis, assess tumor grade and morphology, and carry out biomarker evaluation for expression of estrogen receptor (ER) and progesterone receptor (PR) and HER2 proteins and potentially HER2 gene amplification. Suspi cious axillary lymph nodes should also be biopsied via image-guided techniques. It is important to image both breasts because up to 3% of women with newly diagnosed breast cancer have unsuspected con tralateral disease. Evaluation of the breasts with MRI after a biopsyproven diagnosis is controversial. On the one hand, MRI is more sensitive than radiologic mammography and will commonly detect previously unidentified disease. On the other hand, this observation may lead to additional surgery, including mastectomy, without obvious improvements in outcomes. Staging is a cornerstone for breast cancer management because it provides information about natural history and informs decisions about therapy. The traditional TNM (tumor-node-metastasis) staging system

has evolved to consider molecular testing including biomarkers as above and certain genomic tests such as the Oncotype 21 gene assay. Staging may take place at time of diagnosis (c or clinical staging) or after surgery (p or pathologic staging) or after preoperative systemic therapy followed by surgery (designated with a “y” prefix). For most asymptomatic individuals presenting with early breast cancer, a careful history and physical exam will be sufficient, and testing can be limited to breast imaging and any testing needed to ensure a safe surgical procedure. Individuals who present with symptoms suggestive of meta static disease or physical findings of more advanced disease (e.g., large

Diagnostic Evaluation of the Breast Suspicious clinical breast finding Suspicious breast finding Diagnostic breast imaging mammography ultrasonography MRI (if indicated) Negative/benign Ductal carcinoma in situ with microcalcifications Follow-up exam Uncertain or clinical suspicion persists Resolved Refer to experienced breast diagnostician Routine follow-up screening mammogram as indicated FIGURE 84-2 Evaluation and workup of breast lesions. For more extensive details, see https://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf. (Mammographic images courtesy of Drs. Mark Helvie and Colleen Neal, Department of Radiology, Michigan Medicine. Photomicrographs courtesy of Dr. Celina Kleer, Department of Pathology, Michigan Medicine.) tumor, skin changes, extensive regional adenopathy) should undergo radiologic imaging with computed tomography and radionuclide scanning to look for overt metastatic disease. Suspicious lesions should be biopsied whenever possible to confirm a diagnosis of metastatic breast cancer because of the implications for prognosis and selection of therapy. Less than 10% of patients present with de novo metastatic breast cancer. Breast cancer staging is currently carried out according to the guide lines of the American Joint Committee on Cancer (AJCC) eighth edi tion. Conceptually, stages I and II represent early-stage disease, which is confined to breast and ipsilateral nodes, whereas stage III comprises locally advanced breast cancer and stage IV denotes de novo meta static breast cancer, designated as M1 in the current staging system. Common sites for breast cancer metastasis include soft tissues, lung, bone, liver, and brain. One study suggested that M1 disease can be further divided into at least four subgroups with substantially different prognoses, based on sites and burden of disease as well as biological features. However, these findings have not yet been incorporated into the formal AJCC staging system. Outcomes are directly related to stage at presentation and vary by race and ethnicity in the United States, as shown in Table 84-1.

Screening breast imaging No suspicious breast finding Suspicious mass Suspicious microcalcifications Routine follow-up screening mammogram as indicated CHAPTER 84 Confirmed suspicious finding Invasive ductal carcinoma Biopsy Breast Cancer Progesterone receptor (PR) positive HER2 negative Estrogen receptor (ER) positive CURRENT UNDERSTANDING OF BREAST CANCER BIOLOGY AND CLINICAL IMPLICATIONS It is now accepted that invasive breast cancer is in fact a disease with diverse subtypes, both histologic and molecular. Two decades of molecular analyses have documented multiple transcriptional, epi genetic, and genetic changes that characterize invasive breast cancer. TABLE 84-1 Five-Year Breast Cancer Relative Survival Rate (%) by Stage at Diagnosis and Race/Ethnicity in United States from 2012–2018a STAGE ALL WHITE BLACK AIAN HISPANIC API I

> 99 99 99 99 99 99 II

III

IV

aRace is exclusive of Hispanic origin. Abbreviations: AIAN American Indian/Alaska Native; API Asian/Pacific Islander. Source: Adapted from AN Giaquinto et al: Breast cancer statistics, 2022. CA Cancer J Clin 72:524, 2022.

This has led to the division of invasive breast cancer into at least four major molecular subtypes. Luminal A and B subtypes both express ER and are viewed as generally likely to be responsive to antiestrogen strategies (also called hormonal or endocrine therapies). However, luminal B tumors are characterized by other findings such as reduced PR expression or increased proliferation, usually measured by expres sion of Ki67, and are associated with a poorer outcome than luminal A tumors. The HER2 subtype expresses HER2 protein at high levels and is more likely to benefit from the use of HER2-targeted therapies. Basal tumors tend to lack expression of ER, PR, and HER2 proteins (TNBC). TNBCs carry a poorer prognosis and are generally managed with chemotherapy and immunotherapy. TNBC can be further divided into at least six subtypes, which may also have therapeutic implications, especially in the metastatic setting.

Pathologic evaluation of a breast cancer specimen begins with an assessment of morphology. Most invasive breast cancers are ductal, but about 10–15% are lobular histologies. Lobular cancers are usually ER positive and HER2 negative. They are distinguished by absence of E-cadherin staining or function, and they have a different natural his tory, with a propensity to spread to serosal surfaces, including omen tum, pleura, and meninges or to various parenchyma, such as ovaries and upper and lower gastrointestinal tracts. This curious site for meta static recurrence may result in unusual clinical presentations that may delay diagnosis if metastatic disease is not considered. Other special subtypes are also recognized such as mucinous, medullary, papillary, and metaplastic histologies. Mucinous and pure medullary cancers (distinguished by high levels of lymphocytic invasion surrounding the tumor) are associated with very favorable prognoses with local therapy only. Metaplastic cancers may present as very poorly differentiated tumors or even as squamous or sarcomatoid differentiations. They are generally approached as ductal cancers but may be treated in a manner consistent with their relative subtypes, such as squamous or sarcoma-like differentiation. Tumor grade is also assessed using stan dard approaches such as Nottingham grade, ranging from grade 1 to 3; higher grade is generally associated with poorer prognosis. PART 4 Oncology and Hematology Further profiling of the primary tumor specimens may follow depending on the clinical circumstances. Early-stage ER-positive breast cancers are often evaluated by genomic transcriptional profiling assays to identify patients with such a favorable prognosis that adjuvant chemotherapy in addition to endocrine therapy is not needed; five of these are recommended by the American Society of Clinical Oncol ogy: Oncotype Dx (21 genes), MammaPrint (70 genes), ProSigna (50 genes), EndoPredict (12 genes), and Breast Cancer Index (two genes plus a proliferation signature). Although any one of these appears to be relatively accurate in terms of prognosis, they do not measure the same thing and they have not been compared head-to-head. Therefore, ordering more than one assay for a single case is discouraged.

At pres ent, more detailed molecular analysis is usually restricted to metastatic tumor specimens to identify molecular alterations that are associated with response to specific targeted therapies, as discussed in the section on treatment of metastatic breast cancer. TREATMENT Breast Cancer MANAGEMENT OF IN SITU BREAST CANCER Ductal Carcinoma In Situ (DCIS) Routine use of screening mam mography has led to a marked increase in the diagnosis of DCIS and LCIS. Untreated DCIS (which is confined to the duct without evidence of invasion through the basement membrane into sur rounding interstitial tissue) is associated with a 30% risk of devel oping a subsequent invasive cancer in the same breast. Therapy is generally focused on excision of the lesion to negative margins and to confirm absence of invasion; evaluation of axillary lymph nodes is not generally undertaken. Excision may be followed by radiother apy to the ipsilateral breast and consideration of endocrine therapy if the DCIS expresses ER protein to reduce risk of breast recurrence

or contralateral primary. Patients with extensive DCIS may require mastectomy, whereas those with a small disease burden may opt for excision alone with regular mammographic surveillance. Molecular assays that can predict lack of benefit from radiotherapy after exci sion are sometimes used. Lobular Carcinoma In Situ (LCIS) LCIS is often an incidental find ing on a breast biopsy done for abnormalities on physical exam or mammography. It is viewed as a marker for increased risk of devel oping invasive breast cancer as about 25–30% of women with LCIS subsequently develop invasive disease in either breast. The primary management is continued breast cancer screening and consider ation of chemoprevention with tamoxifen or aromatase inhibitor to decrease risk of invasive disease. Bilateral prophylactic mastectomy is sometimes considered but should be generally limited to those who have other risk factors or concerns. TREATMENT OF EARLY-STAGE BREAST CANCER Multidisciplinary care is a cornerstone for optimal treatment of early breast cancer. The current approach to treatment of earlystage breast cancer reflects evolution from the initial concept of breast cancer as an orderly disease that spreads from breast to axillary nodes to systemic disease to our current understanding of breast cancer as a potentially systemic disease almost from onset. Therefore, treatment approaches incorporate surgery and radiation to treat local disease and systemic therapy to eliminate or suppress any microscopic distant disease. The goal of these treatments in early-stage disease is reduction of subsequent distant recurrence and mortality. They are given in a manner to optimize efficacy while minimizing toxicity and avoiding overtreatment. Surgery Six randomized trials have demonstrated equivalent sur vival with the use of breast-conservation therapy (lumpectomy and, usually, radiotherapy to the remaining breast) or modified radical mastectomy for individuals with early-stage breast cancer. Contra indications to breast conservation include patient preference, poor cosmesis, multifocal disease, previous chest radiation, and ongoing pregnancy that prevents timely administration of radiotherapy. Though not an absolute contraindication, germline mutation in a member of the BRCA gene family can drive a decision for bilat eral mastectomy because of the high risk of subsequent disease in either breast. Patients who require or choose mastectomy should be informed about availability of immediate or delayed reconstruction options using autologous tissue or implants as clinically appropri ate. It is clear, though, that most women with early breast cancer are well served by a lumpectomy to negative margins with axillary management, followed by radiation as appropriate. Management of the ipsilateral axilla continues to evolve as well. For patients with small tumors and clinically negative axillary nodes, sentinel node localization is used to identify clinically rel evant nodes for removal and pathologic assessment to finalize stag ing and inform decisions about extent of radiotherapy and selection of adjuvant systemic therapy. Use of axillary dissection (removal of

level 1 and 2 lymph nodes) is restricted to individuals with palpable lymph nodes or those with substantial pathologic involvement of sentinel lymph nodes. Randomized trials have shown excellent outcomes with omission of any sentinel node evaluation for older women with small biologically favorable tumors and clinically negative axilla who will take adjuvant endocrine therapy as well as omission of axillary dissection for women with low tumor burden in sentinel nodes who will receive radiation. Radiation As with surgery, the use of postoperative radiotherapy to minimize breast recurrence and nodal recurrence has also changed as a result of data accumulated from serial clinical trials. Current treatment strategies are tailored to the individual based on age, tumor size, and nodal status. Options for external-beam radiotherapy include a standard scheme of daily whole breast radiotherapy (WBR) for 4–6 weeks, hypofractionated schedules lasting 5 days to 3 weeks, or partial breast radiation, usually given in

a hypofractionated regimen. Clinical trials of the latter have failed to demonstrate its benefit over WBR. Extension of the radiotherapy port to include regional and axillary nodes is also considered based on pathology and type of surgery. The safety of omitting radio therapy for women older than 65 with low-risk ER-positive tumors who will take endocrine therapy has been demonstrated. Brachy therapy to apply a radiation source directly to the tumor bed is also employed in some cases as a way of shortening duration of therapy. Patients who undergo mastectomy may also benefit from chest wall radiotherapy to reduce risk of both local and distant recur rence, thus improving survival. Potential candidates include those with large tumors or positive axillary lymph nodes, especially those with four or more involved nodes, while those with one to three positive nodes or close/minimally involved margins are also considered. Systemic Therapy It has been recognized that breast cancer is often a systemic disease at time of diagnosis. Enhanced understand ing of breast cancer biology, including the concept that resistant clones evolve as a function of random mutations over time, and the identification of multiple targets of therapy have greatly refined our understanding of the role of systemic therapy in early breast cancer. Such therapy may be given preoperatively (neoadjuvant) or postoperatively (adjuvant) and may take the form of cytotoxic chemotherapy, endocrine therapy directed toward ER, and other targeted therapies such anti-HER2, poly (ADP-ribose) polymerase (PARP) inhibitors in cancers with BRCA1/2 mutations, and/or immunotherapy directed toward immune checkpoints. Treatment algorithms are constantly evolving based on results from clinical trials, and current evidence-based guidelines are available through groups like the National Comprehensive Cancer Network, American Society of Clinical Oncology, or European Society of Medical Oncology. SELECTION OF NEOADJUVANT VERSUS ADJUVANT SYSTEMIC THERAPY The primary goal of neoadjuvant therapy (also designated “pre operative” adjuvant therapy) compared to classic postoperative adjuvant therapy is to downsize tumor to make it more amenable to surgery. A second goal is to provide an in vivo assessment of tumor response to the selected systemic therapy and perhaps direct subsequent adjuvant therapy. Data suggest that individual patients who attain a complete pathologic response (pCR) to neoadjuvant therapy have a better outcome than those who do not, although randomized trials of adjuvant versus neoadjuvant therapy have not shown a difference in survival. At least one trial has demonstrated that patients who fail to experience a pCR to standard combination chemotherapy containing an anthracycline, an alkylating agent, and a taxane, especially those with TNBC, appear to benefit from subsequent capecitabine. Currently, neoadjuvant therapy with che motherapy and anti-HER2 agents is considered for individuals with HER2-positive tumors that are ≥2 cm or node-positive dis ease, while neoadjuvant therapy with chemotherapy and possibly the checkpoint inhibitor pembrolizumab are considered for indi viduals with TNBC ≥2 cm or node-positive disease.

Neoadjuvant endocrine therapy can be used for postmenopausal women with ER- or PR-positive breast cancer to reduce extent of surgery or per haps avoid surgery for older women with multiple comorbidities. Women with small tumors of any subtype are often better served by initial surgery to establish pathologic stage followed by tailored selection of systemic therapy. Types of Systemic Therapy for Early Breast Cancer Endocrine therapy is a mainstay for management of ER- and/or PR-positive invasive breast cancer; positive tumors are commonly defined as those with ≥1% staining by immunohistochemistry. Because of their mechanisms of action as blockers of interaction between estrogen ligand and ER, the selective ER modulators tamoxifen and toremi fene can be used in women with any menopausal status. In contrast, estrogen deprivation approaches depend on menopausal status.

The use of aromatase inhibitors, such as anastrozole, letrozole, and exemestane, as monotherapy is restricted to postmenopausal women. Ovarian suppression by gonadotropin hormone–releasing hormone (GnRH), such as the luteinizing hormone–releasing hormone (LHRH) agonists goserelin or leuprolide, or alternatively surgical oophorectomy, can be used to reduce circulating estradiol levels in premenopausal women to postmenopausal levels. These women can then also be treated either with tamoxifen or an AI. The CDK4/6 inhibitors abemaciclib and ribociclib may be used in combination with endocrine therapy for high-risk, early-stage, ERpositive breast cancer.

Multiple cytotoxic agents have shown efficacy for treatment of metastatic breast cancer and are now used in treatment of early-stage disease. The most common regimens include cyclophosphamide, doxorubicin, paclitaxel, docetaxel, 5-fluorouracil, methotrexate, and/ or one of the platin salt compounds (cisplatin or carboplatin). Several anti-HER2 therapies are also available. Two monoclonal antibodies, trastuzumab and pertuzumab, and two tyrosine kinase inhibitors, neratinib and lapatinib, are approved for use in earlystage breast cancer; multiple other agents are available for meta static disease, as discussed below, and are undergoing testing for use in earlier stages of disease. CHAPTER 84 The role of immunotherapy with the checkpoint inhibitors is also under evaluation. At present, pembrolizumab for patients with TNBC is the only U.S. Food and Drug Administration (FDA)- approved agent for early-stage breast cancer, but others are under investigation. A targeted agent, olaparib, an oral PARP inhibitor, is also used as an adjunct to chemotherapy for women with high-risk, germline BRCA-mutated, HER2-negative breast cancer who have completed (neo)adjuvant chemotherapy. It is particularly active in cancers with DNA repair pathway defects. Breast Cancer GENERAL GUIDELINES FOR (NEO)ADJUVANT SYSTEMIC THERAPY FOR EARLY BREAST CANCER Approach to ER- and/or PR-Positive Breast Cancer Endocrine therapy is the foundation for adjuvant therapy for women with ER- and/or PR-positive breast cancer. Selection is based on menopausal status and consideration of side effect profiles. For premenopausal women with low-risk breast cancer, tamoxifen for 5–10 years is the standard. Premenopausal women with higher risk tumors are candidates for combined endocrine therapy with an LHRH agonist plus tamoxifen or aromatase inhibitor for 5 years. Multiple random ized trials have shown that aromatase inhibitors for 5 years provide modest but statistically significant superior outcome compared with tamoxifen for postmenopausal women. Women with ERpositive breast cancers are at risk for distant recurrence long after their original diagnosis, from 10–20 or more years. Some trials suggest that up to 10 years of endocrine therapy may be indicated for healthy postmenopausal women with higher risk tumors and good tolerance. Given the chronic nature of adjuvant endocrine therapy, careful attention to side effects is warranted. Tamoxifen is associated with postmenopausal symptoms and a small chance of thromboembolic events or

uterine cancer, especially in women over 50 years. Aro matase inhibitors are associated with postmenopausal symptoms, arthralgias, and bone loss, while LHRH agonists are associated with postmenopausal symptoms and bone loss. Although the three aromatase inhibitors appear to be equally effective, tolerance may vary; patients who are intolerant of one aromatase inhibitor may benefit from change to another member of the family or tamoxifen. A critical decision in this setting is the value of chemotherapy in addition to endocrine therapy. Its absolute (as opposed to relative or proportional) benefit varies by menopausal status and nodal status. Genomic multigene expression testing of the tumor with assays like Oncotype, MammaPrint, ProSigna, EndoPredict, or Breast Cancer Index will identify a substantial portion of patients with zero to three positive nodes who would not benefit from adjuvant chemotherapy.

Neoadjuvant chemotherapy should be administered to healthy individuals with a large tumor burden or more than three positive nodes, especially premenopausal patients with a primary goal of reducing tumor size. However, in ER-positive disease, the likeli hood of a pCR is low. Regardless, adjuvant chemotherapy (neoad juvant or standard) is considered for healthy individuals with four or more positive lymph nodes as well as for those with lesser nodal burden who have high genomic signature score. Established chemo therapy regimens are outpatient based and use multiple agents for 3–6 months with appropriate supportive care including antiemet ics and colony-stimulating factors as appropriate to reduce risk of febrile neutropenia. Long-term side effects can include premature menopause in premenopausal women and a small risk of doxorubicinrelated cardiomyopathy, taxane-related peripheral neuropathy, or secondary leukemia, and possible cognitive dysfunction.

Women with node-positive or high-risk node-negative, ER- and/ or PR-positive, HER2-negative breast cancer who have completed adjuvant chemotherapy should consider use of a CDK4/6 inhibi tor in conjunction with endocrine therapy. Current information supports the use of abemaciclib for 2 years or ribociclib for 3 years; addition of palbociclib for 2 years did not improve outcomes. Those with HER2-negative germline BRCA-mutated breast cancer who have received (neo)adjuvant chemotherapy should consider a year of oral olaparib. When used in conjunction with chemotherapy or anti-HER2 therapy, endocrine therapy is generally delayed until completion of adjuvant chemotherapy to minimize toxicity. PART 4 Oncology and Hematology Approach to HER2-Positive Breast Cancer Healthy individuals with tumor ≥3 cm or positive lymph nodes are candidates for neo adjuvant therapy with multiagent chemotherapy and trastuzumab with or without pertuzumab for 4–5 months. Those who achieve a pCR should receive further trastuzumab with or without pertu zumab therapy to complete a year. By contrast, those with residual invasive disease at surgery should switch to complete a year of the antibody-drug conjugate (ADC) trastuzumab emtansine (TDM-1). High-risk individuals who have completed a year of anti-HER2 therapy can also consider addition of oral neratinib for another year, although the benefits are incremental. Toxicity of trastuzumab is relatively uncommon. Few patients have any side effects during treatment. However, the greatest risk is reduction of cardiac ejection fraction. Therefore, baseline cardiac evaluation with an echocardiogram should be obtained, and trastu zumab should not be given to those with low ejection fraction, or they should be evaluated by an experienced cardiologist if therapy is felt to be critical. Serial echocardiograms should be obtained during adjuvant trastuzumab therapy but are not indicated once therapy is discontinued if the patient has not had any evidence of cardiac dysfunction. Pertuzumab is commonly associated with loose stools or diar rhea. This can be managed with conservative loperamide treatment. However, the added

benefit of adjuvant pertuzumab to trastuzumab is modest, and if diarrhea is not easily controlled, trastuzumab should be continued alone. Individuals who present with smaller tumors with clinically neg ative nodes should be considered for upfront surgery to establish pathologic stage. This is because women with pathologically nodenegative tumors <3 cm have excellent outcomes with a regimen of single-agent weekly paclitaxel for 12 weeks in conjunction with a year of trastuzumab with or without pertuzumab. Patients with HER2-positive tumors that are ER and/or PR posi tive should receive endocrine therapy as described above. Endocrine therapy is generally initiated after completion of any chemotherapy and can be given concurrent with anti-HER2 therapy. Neither CDK4/6 inhibitors nor PARP inhibitors have been tested as an adju vant therapy in early-stage HER2-positive breast cancer. Triple-Negative Breast Cancer (TNBC) Healthy patients with early-stage TNBC are frequently candidates for (neo)adjuvant che motherapy. Those with tumors >2 cm or tumors >1 cm and positive axillary nodes should be considered for neoadjuvant multiagent

chemotherapy, perhaps in conjunction with the checkpoint inhibi tor pembrolizumab. If chemoimmunotherapy is utilized, then pem brolizumab is continued postoperatively to complete a year. Those who achieve a pCR receive pembrolizumab alone. Those patients who do not have a pCR may also consider further chemotherapy with capecitabine. In contrast, those with smaller tumors that are clinically node negative are best served by initial surgery to estab lish pathologic stage, which might permit a refinement of choice of chemotherapy regimen. Follow-Up of Survivors of Early-Stage Breast Cancer Asymp tomatic survivors of early-stage breast cancer should be followed regularly with history and physical examination to look for any evidence of recurrent disease and to assess for toxicities of prior or ongoing treatments. These exams are conducted every 3–6 months for the first 3 years and diminish in frequency over time. As noted, serial echocardiograms beyond 12 months of trastuzumab therapy are not needed. Annual breast imaging to look for ipsilateral or contralateral disease is the only routine testing needed. In the absence of symptoms or physical exam findings, routine imaging of other types or blood studies have not been shown to enhance wellbeing or outcome from breast cancer. Current research is focused on use of blood-based assays for circulating tumor cells (CTCs) or circulating free tumor DNA (ctDNA) as markers for early detection of recurrent disease, but these are investigational approaches at present. As many patients have long survival, routine follow-up by a primary care provider and adherence to age-appropriate general health guidelines are key. Symptom management is a key aspect of follow-up, especially for those on adjuvant endocrine therapy as adherence is a crucial determinant of outcome. Hot flashes may be ameliorated by use of antidepressants like venlafaxine or gabapentin, while vaginal dry ness should be addressed through topical agents or, if unsuccessful, vaginal estrogen. Avoidance of hormone replacement therapy is preferred. Aromatase inhibitor–associated musculoskeletal symp toms may be treated by switching from one aromatase inhibitor to another after a 4- to 6-week washout period, or they can be addressed by exercise, nonsteroidal anti-inflammatory agents, acu puncture, or the antidepressant duloxetine. Persistent taxane-related peripheral neuropathy is sometimes responsive to gabapentin. Special Considerations in Management of Individuals with Early Breast Cancer

Use of Bisphosphonates Bone health can be compromised by breast cancer therapy, especially the estrogen-deprivation agents, aromatase inhibitors and LHRH agonists. Patients who receive these therapies may benefit from use of a bisphosphonate, zoledro nate every 6 months for 3 years, or oral clodronate or ibandronate as a bone-strengthening agent. In addition, a meta-analysis suggests that this therapy is associated with decreased breast cancer recur rence, especially in

bone. Data on denosumab are less compelling at present. Pregnancy, Fertility, and Childbearing in Premenopausal Women The diagnosis of breast cancer during pregnancy can be difficult because of the evolving changes in the pregnant breast. Suspicious lumps or skin or nipple changes should be evaluated as above though imaging modalities of choice including ultrasound or MRI. If breast cancer is diagnosed and pregnancy is continued, the goal is to administer appropriate multimodality therapy to optimize maternal outcome from breast cancer and minimize toxicity to the fetus. Breast surgery can be safely undertaken during the second and third trimesters, but any therapeutic radiation must be delayed until after delivery. If indicated, certain chemotherapy agents such as doxorubicin and cyclophosphamide can be administered during the second and third trimesters, whereas others such as methotrex ate and 5-fluorouracil should be avoided. In general, endocrine and targeted therapies should not be used until after delivery. Comanagement by experienced multidisciplinary breast cancer and high-risk obstetrical teams is preferred.

Diagnosis of breast cancer in all premenopausal women neces sitates discussion about fertility preservation and pregnancy with those women who desire later pregnancy. Premature menopause is a known consequence of adjuvant chemotherapy, and likeli hood is related to type and duration of chemotherapy and age of patient. It is seen in <50% of women <40 years old but is common in those who are over 40. Patients are asked to avoid pregnancy while on adjuvant endocrine therapy. Thus, counseling about and implementation of fertility-preservation techniques are a priority in newly diagnosed premenopausal women if further childbearing is planned. A meta-analysis suggests that concurrent administration of an LHRH agonist to suppress ovarian function during adjuvant chemotherapy may help to preserve subsequent ovarian func tion without adverse breast cancer outcomes. Avoidance of oral contraceptives or hormone-based intrauterine devices is recom mended for premenopausal breast cancer survivors who require contraception. Though data are not extensive, pregnancy after early stage breast cancer diagnosis appears to be safe. There is no evidence of increased rate of recurrence compared to matched patients who did not become pregnant, nor is there evidence of increased fetal anom alies. A recent study has documented the safety and pregnancy success rate for women with treated early ER-positive breast cancer who stop adjuvant tamoxifen after 18–24 months of therapy and then resume after pregnancy to complete their prescribed course. Male Breast Cancer Men with breast cancer usually present with a breast lump or other physical abnormality. Principles about diagnosis, staging, and local therapy are like those for women, although most men undergo mastectomy for primary management for anatomic reasons. Men with breast cancer should undergo genetic testing as germline BRCA mutation is seen in up to 14% of men with breast cancer. About 90% of male breast cancers express ER, and adjuvant endocrine therapy is standard. Tamoxifen is the drug of choice; if an aromatase inhibitor is indicated (as for example in an individual who has a history of thromboembolic disease), concomitant administration of an LHRH agonist is required. Guidelines for use of adjuvant chemotherapy are like those for postmenopausal women. LOCALLY ADVANCED BREAST CANCER In the United States, about 10% of patients present with locally advanced or stage III breast cancers, although this presentation is more common in less-resourced countries. These tumors are characterized by a large primary tumor, involvement of skin or chest wall, or fixed tumors or axillary lymph nodes, findings that make primary surgical resection difficult or impossible. Inflam matory tumors that present with rapid onset of erythema, swelling, and tenderness of the breast are a subset of locally advanced breast cancer and are sometimes confused with mastitis or other infection. Breast or skin biopsy is critical in the setting of breast inflammation that fails to resolve after antibiotics. Skin biopsy showing dermal lymphatic invasion

with tumor cells is often associated with the diagnosis of inflammatory breast cancer. Because up to one-third of these patients have detectable metastasis at time of diagnosis, an evaluation for metastatic disease is recommended even in asymp tomatic patients. Combined-modality therapy begins with neoadjuvant systemic therapy, whose selection is guided by biomarker status as outlined above, to downstage tumor to permit resection. Mastectomy with axillary dissection is often required in the case of inflammatory or other T4 lesions because breast-conserving therapy has been associ ated with an unacceptably high incidence of locoregional recurrence. Postoperative radiotherapy is the norm in conjunction with systemic therapy with chemotherapy and/or anti-HER2 therapy and/or endo crine therapy tailored to the biological qualities of the tumor. METASTATIC BREAST CANCER Presentation and Evaluation About 20–25% of patients who are treated for early breast cancer subsequently develop metastatic

disease, presumably because of micrometastatic disease at time of diagnosis that was or becomes resistant to adjuvant systemic therapy. Metastatic disease can be detected years to decades after primary diagnosis, especially in the setting of ER-positive disease, whereas it is most likely to be diagnosed within 3–7 years after treatment for TNBC or ER-negative/HER2-positive breast cancer. Only about 5% of patients present with de novo metastatic or stage IV breast cancer in the United States.

Patients may present with abnormal physical exam or symptoms suggestive of metastases. As shown in Fig. 84-3, careful evaluation of extent of disease with computed tomography and radionuclide imaging, routine blood studies, and measurement of tumor mark ers such as carcinoembryonic antigen (CEA) and either CA27/29 or CA15-3 should be undertaken. Wherever possible, it is critical to biopsy a suspicious lesion to confirm the diagnosis of metastatic breast cancer and assay tumor markers including ER, PR, and HER2 because they may have changed from the initial biopsy under the pressure of time or therapy. In addition, PD-L1 staining and tumor mutational burden should be assessed in tumor, and assays for PIKC3A and ESR1 mutations should be performed in blood or tumor to delineate options for treatment. Next-generation sequenc ing of tumor may also be considered to simultaneously survey for any other targetable changes to guide selection of therapy or eligi bility for a clinical trial. CHAPTER 84 Goals of Care and General Management Metastatic breast cancer is rarely curable, and the goals of therapy, which is chronic—to palliate or prevent symptoms without undue toxicity—should be explicitly discussed with the patient at the time of diagnosis of metastatic disease. Median survival is <3 years, although the range is wide. Some patients with favorable characteristics such as ERpositive disease, nonvisceral disease, long disease-free interval, and good performance status may survive using serial therapies for many years, whereas those with TNBC are more likely to progress sooner and succumb to their disease. Advances in our understand ing of biology of ER- and HER2-positive and genetically mutated (e.g., BRCA1/2, PIK3CA) breast cancer and development of a myriad of targeted treatments have led to improved outcome for these subtypes in recent years. Breast Cancer Unlike in early breast cancer, the primary intervention in meta static breast cancer is systemic therapy. Surgery is generally limited to excision of isolated local recurrence or a solitary brain metastasis or stabilization of a bone metastasis. Randomized trials suggest that patients who present with de novo metastatic breast cancer do not have improved outcomes with surgical treatment for the primary breast cancer in addition to systemic therapy and the focus should be on systemic therapy. Radiotherapy may be used at any time to palli ate symptomatic localized disease such as bony or brain metastases. All patients with metastatic breast cancer should have access to

palliative therapy approaches in addition to antineoplastic therapy to maximize symptom control and quality of life. In addition, those with metastatic bone disease should be considered for regular administration of bisphosphonate or denosumab in addition to antineoplastic therapy to reduce the chance of skeletal morbidity including pain, fracture, and need for radiotherapy. Patients with metastatic breast cancer require regular followup with history and physical exam to gauge response to therapy. Patient well-being and relief of symptoms are paramount, and use of imaging and blood studies should be personalized to the patient and therapy to adjust dose or schedule and to assist in decisions about efficacy and toxicity of therapy. Current algorithms suggest changes in therapy only if the patient has clear signs of disease progression or unacceptable toxicity. Studies to evaluate the role of serial liquid biopsies to track CTC or ctDNA as an indicator to switch therapy, and even to switch to a targeted therapy suggested by the mutational profile of the ctDNA, in the absence of clinical or radiologic evidence of disease progression are in progress. Management of ER-Positive Metastatic Breast Cancer Whenever possible, serial use of endocrine therapy is the preferred approach

Clinical symptom History, physical exam Suspicious history or clinical finding Diagnostic workup Imaging as indicated (direct image of suspicious site; anatomic imaging: CT or MRI; scintigraphic imaging: bone or PET scan) blood tests as indicated (CBC, liver function tests, circulating tumor biomarkers: CA15-3 or 27.29; CEA) Confirmed suspicious finding Nondiagnostic Follow-up evaluation Biospy if possible PART 4 Oncology and Hematology Resolved Uncertain or persists Routine follow-up Routine follow-up Continue follow-up rule out noncancer etiology repeat diagnostic workup if indicated FIGURE 84-3 Evaluation of new signs or symptoms in a patient with prior history of early-stage breast cancer. See text for details. CBC, complete blood count; CEA, carcinoembryonic antigen; ER, estrogen receptor; NGS, next-generation sequencing; PET, positron emission tomography; PgR, progesterone receptor. to patients whose recurrent tumor is ER and/or PR positive and whose clinical presentation is not dire. Use of chemotherapy can be reserved for those with life-threatening visceral disease like lymphangitic lung metastases or impending liver failure. However, a prospective trial has suggested that overall survival was the same in patients with apparent rapidly growing visceral disease ran domly assigned to either chemotherapy or endocrine therapy and a CDK4/6 inhibitor. There is no value for concurrent endocrine therapy and chemotherapy for management of metastatic breast cancer. Selection of type of endocrine therapy will depend on menopausal status and previous adjuvant endocrine therapy. It may be paired with targeted therapy depending on the molecular profile of the cancer and clinical scenario. For the uncommon patient who presents with untreated ER-posi tive metastatic breast cancer, therapy generally begins with aromatase inhibitor plus CDK4/6 inhibitor for postmenopausal women and LHRH agonist plus aromatase inhibitor plus CDK4/6 inhibitor for premenopausal women; median progression-free survival is about 2 years, and median overall survival is >3 years with this approach. More commonly, patients present with recurrent disease diag nosed while on or after completing adjuvant endocrine therapy. For those who have received aromatase inhibitor, up to one-half will have evidence of ESR1 mutation and may be candidates for the oral selec tive estrogen receptor degrading (SERD) agent elacestrant if they have also received a CDK4/6 inhibitor. Those without evidence of ESR1 mutation are often treated with an alternate SERD, fulvestrant, which is administered monthly by intramuscular injection; this may be coupled with a CDK4/6 inhibitor if the patient has not previously received such an agent. The value of continuing or switching to another CDK4/6 inhibitor for those who have previously received adjuvant CDK4/6 inhibitor is not clearly defined in this setting. For postmenopausal patients previously treated with

endocrine therapy who are found to have a PIKC3A mutation by liquid or tissue biopsy, the use of alpelisib (a selective inhibitor of PI3Kα) with fulvestrant can be considered. Postmenopausal patients with

Other cancer or condition Positive for metastases Benign Further evaluation and treatment as indicated Re-evaluate tumor biomarker status ER, PgR, HER2, PIK3CA mutation, PD-L1, NGS (tissue or circulating) PIK3CA/AKT1/PTEN alterations who have received one endocrine therapy for metastatic disease or recur within 12 months of complet ing adjuvant therapy can receive capivasertib (a pan-AKT inhibitor) with fulvestrant. The use of aromatase inhibitor plus everolimus, an mTOR inhibitor, can be considered for patients without targetable mutations as it, too, has been shown to increase progression-free survival over endocrine therapy alone. Each of these targeted agents carries a unique set of toxicities, and careful monitoring of clinical status and blood studies is needed for safe administration. Other approaches, especially for patients who have demonstrated repeated and lengthy responses to serial hormone therapies, can include switch to another aromatase inhibitor or tamoxifen or administration of additive hormone therapies such as progestins, androgens, and estrogens. The latter category of agents is seldom used at present because of concerns about toxicity and the advent of newer more targeted therapies. At some point, it will become apparent that a patient has tumor that is unresponsive to endocrine therapy, which necessitates a transition to other types of systemic therapy. The timing of this decision may be informed in part by the observation that likelihood of disease control and the duration of benefit are decreased by about one-half with each successive switch in endocrine therapy. Management of Endocrine-Unresponsive ER-Positive, HER2-Negative Breast Cancer or TNBC Chemotherapy is the backbone of sys temic therapy for individuals with metastatic HER2-negative breast cancer that is not responsive to endocrine therapy. Unlike in the setting of early breast cancer where multiagent chemotherapy is the norm, use of combination chemotherapy in metastatic breast cancer should be reserved for the uncommon situation of visceral crisis where a rapid reduction in tumor burden is desirable. For most patients, serial use of single-agent chemotherapy is associated with an acceptable likelihood of disease palliation without excess toxic ity; combination chemotherapy does not improve overall survival over sequential monotherapy.

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