

BREAST CANCER

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Invasive breast cancer, the most common nonskin cancer in women in the United States, will be diagnosed in approximately 235,000 women in this country in 2013 and is expected to result in approximately 40,000 deaths.¹ Incidence and mortality reached a plateau and appear to be dropping in both the United States and parts of western Europe.² This decline has been attributed to several factors, such as early detection through the use of screening mammography and appropriate use of systemic adjuvant therapy,³ as well as decreased use of hormone replacement therapy.⁴ However, the global burden of breast cancer remains great, and global breast cancer incidence increased from 641,000 in 1980 to 1,643,000 in 2010, an annual rate of increase of 3.1%.⁵

Etiology and Epidemiology

The incidence of breast cancer in the United States increased steadily from World War II to the turn of the 21st century. Multiple risk factors for its development have been identified. Breast cancer is predominantly a disease of women, although it does occur in men, with an incidence of approximately 1% of that seen in women. Chief among the risk factors are advancing age and family history. Incidence increases with age, and about 75% of breast cancer cases in the United States are diagnosed in women older than 50 years. The diagnosis of breast cancer in first-degree relatives younger than 50 years is associated with a threefold to fourfold increased risk. Approximately 5 to 8% of cases of breast cancer occur in high-risk families. Several familial breast cancer syndromes and their associated molecular abnormalities have been identified.⁶ These include the breast-ovarian cancer syndrome, which is attributed to germline mutations in either of two breast cancer susceptibility genes, *BRCA1* and *BRCA2*. These mutations are inherited as an autosomal dominant trait and can therefore be transmitted through both the maternal and the paternal line. Initial linkage studies suggested that a germline mutation in either of these genes was associated with a lifetime risk of breast cancer of up to 85%. However, more population-based studies suggest that breast cancer develops in 50 to 60% of carriers.⁷ Other hereditary breast cancer syndromes are the Li-Fraumeni syndrome, which is associated with germline mutations in the *TP53* tumor suppressor gene,⁸ and Cowden disease, which is linked to inherited mutations in the *PTEN* gene.⁹

Reproductive risk factors include early menarche, late menopause, late first pregnancy, and nulliparity. The common thread in all of these is presumed to be prolonged exposure of the breast to estrogen.¹⁰ Careful study has demonstrated that certain types of breast pathology, such as atypical hyperplasia and lobular carcinoma in situ (LCIS), are also associated with increased risk. Furthermore, certain environmental factors increase the risk of breast cancer.

Financial disclosure information is located at the end of this chapter before the references.

These factors include exposure to ionizing radiation during adolescence,¹¹ prolonged use of hormone replacement therapy¹² (but not estrogen replacement therapy¹³), ongoing use of oral contraceptives,¹⁴ and consumption of alcohol.¹⁵ Large-scale studies have failed to show any convincing linkage between exposure to certain pesticides¹⁶ or a high-fat diet¹⁷ and the development of breast cancer. The possibility that increased breast density as measured by mammography might be associated with enhanced breast cancer risk has been raised.¹⁸

Prevention

CHEMOPREVENTION

There has been much interest in the development of breast cancer prevention strategies. Pharmacologic approaches are the most developed at this time. The nonsteroidal selective estrogen receptor modulator (SERM) tamoxifen, a mainstay in the management of breast cancer, has also been tested as a chemopreventive agent. A large US trial randomized 13,388 high-risk women to receive either tamoxifen or placebo for 5 years.^{19,20} Risk factors for breast cancer used to determine eligibility were age older than 60 years, a diagnosis of LCIS, or age of 35 to 59 years with a constellation of risk factors that, when combined, resulted in a 1.67% or greater risk of breast cancer developing within 5 years. Use of tamoxifen was associated with a reduction in the diagnosis of breast cancer of about 50%; benefit was noted in all age groups. Other effects of tamoxifen are summarized [see Table 1]. As a general rule, an increase in serious adverse events such as endometrial cancer or in thromboembolic events was confined largely to women older than 50 years. On the basis of these data, the Food and Drug Administration (FDA) approved the use of tamoxifen to reduce the occurrence of breast cancer in women at high risk, as defined by the eligibility requirements for this prevention trial. Two other tamoxifen prevention trials, conducted in the United Kingdom²¹ and Italy,²² showed less advantage with tamoxifen; this difference in findings has been attributed to the smaller size and variations in eligibility criteria of the two studies. In particular, the small sample size and lower baseline breast cancer risk may have limited the ability of these trials to detect a tamoxifen effect. A fourth trial, the International Breast Cancer Intervention Study, also showed a reduction in diagnosis of invasive breast cancer in tamoxifen recipients.²³ Initial results from these four trials were analyzed in a meta-analysis that confirmed a 38% reduction in invasive breast cancer with tamoxifen.²⁴ The salient features of reported trials are summarized in Table 2.

Other SERMs have been studied as chemopreventive agents. One such agent, raloxifene, was originally approved for use in the prevention of osteoporosis in postmenopausal

Table 1 Selected Outcomes from the NSABP P-1 and P-2 Chemoprevention Trials^{20,26}

Outcome	Placebo (N = 6,599)	Tamoxifen (N = 6,576)	Risk Ratio (95% CI)	Tamoxifen (N = 9,726)	Raloxifene (N = 9,745)	Risk Ratio (95% CI)
Invasive breast cancer	175	89	0.51 (0.39–0.66)	247	310	1.24 (1.05–1.47)
Endometrial cancer	15	36	2.53 (1.35–4.97)	65	37	0.55 (0.36–0.83)
Other cancers	97	97	1.00 (0.75–1.35)	338	359	NA
Myocardial infarction	28	31	1.11 (0.65–1.92)	NA	NA	NA
Stroke	24	38	1.59 (0.93–2.77)	NA	NA	NA
Pulmonary embolism	6	18	3.01 (1.15–9.27)	84	68	0.80 (57–1.11)
Deep vein thrombosis	22	35	1.60 (0.91–2.86)	118	86	0.72 (0.54–0.95)
Fractures	137	111	0.81 (0.63–1.05)	NA	NA	NA
Cataract development	507	574	1.14 (1.01–1.29)	739	603	0.80 (0.72–0.89)

CI = confidence interval; NA = not available; NSABP = National Surgical Adjuvant Breast and Bowel Project.

women; however, early results from osteoporosis trials suggested that raloxifene may also reduce the risk of breast cancer. One trial in which patients were randomized to receive either raloxifene or placebo showed that the incidence of breast cancer was reduced in postmenopausal women who were at average breast cancer risk and who had an increased risk of cardiovascular disease; raloxifene had no significant effect on the risk of coronary artery disease, but raloxifene was associated with an increased risk of fatal stroke and venous thromboembolism.²⁵ A second trial showed that raloxifene was somewhat less effective than tamoxifen in preventing invasive and noninvasive breast cancer in postmenopausal women at high risk for breast cancer; however, raloxifene was also associated with fewer

thromboembolic events and endometrial cancers²⁶ [see Table 1]. Given the extensive evidence supporting the use of tamoxifen or raloxifene for breast cancer risk reduction and their approval for this purpose by the FDA, it is puzzling that their use is not more pervasive in high-risk women. A simple risk/benefit index to quantify benefits from chemoprevention with tamoxifen or raloxifene in postmenopausal women has been developed to assist in more widespread adoption of prevention strategies.²⁷ Finally, a randomized, placebo-controlled trial of the aromatase inhibitor exemestane or placebo for prevention in high-risk postmenopausal women also demonstrated a 65% reduction in the risk of invasive breast cancer, raising the possibility that this agent may also be used.²⁸

Table 2 Tamoxifen Chemoprevention Trials for Breast Cancer

Trial	Participant Number	Breast Cancer Events	Median Follow-up	Participant Characteristics	Results
NSABP P-1	13,388	358	55 mo	≥ 1.67% 5-year risk of developing breast cancer	49% overall reduction in breast cancer diagnosis in tamoxifen group
				No concurrent HRT	
				76% with first-degree relative	
				39% < 50 yr old	
Italian Randomized Tamoxifen Prevention Trial	5,408	136	11 yr	No requirement for increased risk	No difference in breast cancer diagnosis except in high-risk recipients of tamoxifen
				Concurrent HRT allowed	
				12% with first-degree relative	
				38% < 50 yr old	
Royal Marsden Hospital, UK	2,471	186	13 yr	Increased risk because of family history	22% reduction in invasive breast cancer diagnosis in tamoxifen group (<i>p</i> = .1)
				Concurrent HRT in 26%	
				96% with first-degree relative	
				62% < 50 yr old	
IBIS-1	7,152	337	96 mo	Increased risk because of family history or LCIS	27% reduction in breast cancer in tamoxifen group (<i>p</i> = .004)
				48% had a first-degree relative who developed breast cancer before age 50	
				Median age = 51 yr	

HRT = hormone replacement therapy; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; NSABP = National Surgical Adjuvant Breast and Bowel Project.

LIFESTYLE MODIFICATION

Prevention strategies that involve alterations in lifestyle have been suggested. The Women's Health Initiative did not show a clear advantage for a low-fat diet as a means of breast cancer prevention.¹⁷ Regular exercise, especially during adolescence, may be associated with diminished breast cancer risk. By inference from the epidemiologic studies mentioned above, abstinence from alcohol may slightly reduce the risk of breast cancer.

PROPHYLACTIC MASTECTOMY AND OOPHORECTOMY

Prophylactic mastectomy has been considered as a means of decreasing breast cancer risk, particularly for women at high risk because of a strong family history or carriage of mutant breast cancer susceptibility genes. A prospective multicenter cohort study of 2,482 women with *BRCA1* or *BRCA2* mutations suggested that prophylactic bilateral mastectomy may substantially reduce diagnosis of breast cancer.²⁹ It is critical that women contemplating such an approach be aware of reports of cancer development in remnants of breast tissue after the prophylactic surgery. It is not known whether prophylactic surgery is superior to aggressive screening coupled with appropriate management of any breast cancer that is diagnosed. Prophylactic oophorectomy in mutation carriers has also been shown to decrease breast cancer incidence and mortality significantly in *BRCA* mutation carriers, presumably because of the ablation of ovarian steroids.²⁹

Screening

Screening strategies for breast cancer include the triad of breast self-examination (BSE), clinical breast examination by a health care professional, and screening mammography. Although widely touted as an important component of early detection, BSE is of uncertain value. A large randomized trial that compared conventional BSE with observation in over 260,000 female Chinese textile workers failed to show any clinical advantage with BSE.³⁰ As a consequence, some experts, including the American Cancer Society, now promote breast awareness rather than regular BSE.

In contrast, regular screening by mammography and clinical breast examination appear to decrease mortality from breast cancer by 25 to 30% in women older than 50 years. Considerable controversy continues over the value of screening mammography and clinical breast examination in women 40 to 50 years of age.³¹ A second area of uncertainty is the optimal frequency of mammography. Currently, the American Cancer Society and the National Cancer Institute recommend annual screening mammography for women older than 40 years who are at standard risk for breast cancer, whereas the U.S. Preventive Services Task Force recommends against routine screening mammography in women ages 40 to 49 years and promotes biennial screening mammography for women between the ages of 50 and 74 years.³² No randomized trial has assessed the role of screening mammography in women older than 70 years. However, it would seem reasonable to continue mammography in older women whose life expectancy exceeds 5 years; women whose survival is limited because of other medical conditions are not likely to benefit. There have been

no trials of mammographic strategies directed explicitly at high-risk women, particularly those with *BRCA1* and *BRCA2* mutations. In the absence of relevant data, a reasonable approach is to begin mammographic screening either at 25 years of age or 5 years earlier than the age of the person with the earliest diagnosis of breast cancer in the immediate or extended family. A 2005 study comparing digital mammography with conventional film screen mammography failed to show an advantage for digital mammography overall but suggested that digital mammography may be more effective for women with dense breasts.³³

Much work is focused on the value of ultrasonography, magnetic resonance imaging (MRI), breast tomosynthesis, and technetium-99m sestamibi imaging in screening. Testing of these modalities as screening tools is driven in part by the knowledge that 10 to 15% of breast cancers are not detected by mammography. Evaluation of these modalities as screening tools is of particular interest in women who are at high risk, such as carriers of *BRCA1* and *BRCA2* gene mutations, for whom MRI has been suggested as an effective breast cancer screening technique.³⁴ Furthermore, MRI has been shown to detect breast cancer in the contralateral breast in 3% of women with a newly diagnosed breast cancer whose contralateral mammogram showed no abnormality.³⁵ A randomized trial of detection of breast cancer with the addition of annual screening ultrasonography or a single screening MRI to mammography in women with elevated breast cancer risk showed that the addition of screening ultrasonography or MRI to mammography results in higher cancer detection and an increase in false positive findings. The number of screens needed to detect one cancer was 127 for mammography, 234 for supplemental ultrasonography, and 68 for MRI after a negative mammogram and sonogram.³⁶ The American Cancer Society has recommended consideration of screening MRI for women whose predicted risk of breast cancer development exceeds 20%.³⁷ Use of MRI is limited by the fact that although it is highly sensitive, it lacks specificity. Insufficient information exists about other breast imaging modalities to warrant their use for screening.

Staging and Prognosis

The TNM classification of clinical staging rests on the clinical assessment of tumor size, nodal status, and evidence of metastatic disease. However, pathologic staging is preferable because it provides the most accurate estimate of tumor involvement and prognosis. The staging system for breast cancer is regularly updated.³⁸ Most patients with breast cancer present with stage I or II disease. In these patients, extensive laboratory evaluation is of little value. Studies in the asymptomatic patient with apparent stage I or II breast cancer can be limited to a hemogram, chemistry panel, and chest x-ray. More sophisticated radiologic or laboratory staging is not warranted because of low yield. However, patients with symptoms suggestive of metastatic disease or women with clinical evidence of stage III or IV breast cancer should undergo more intensive evaluation of common sites of metastasis, such as bone, liver, and lung, by use of radio-nuclide scanning and computed tomography (CT). Current staging guidelines are presented in Table 3 and Table 4.

Table 3 TNM Staging System for Breast Cancer³⁸

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of tumor
	Tis	Carcinoma in situ
	Tis (DCIS)	Ductal carcinoma in situ
	Tis (LCIS)	Lobular carcinoma in situ
	Tis (Paget)	Paget disease of the nipple with no tumor
	T1	Tumor ≤ 2 cm
	T1mic	Tumor ≤ 0.1 cm
	T1a	Tumor > 0.1 cm–0.5 cm
	T1b	Tumor > 0.5 cm–1 cm
	T1c	Tumor > 1 cm–2 cm
	T2	Tumor > 2 cm–5 cm
	T3	Tumor > 5 cm
	T4	Tumor of any size with direct extension to chest wall and/or skin
	T4a	Extension to chest wall, not including pectoralis muscle
	T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma
	Regional lymph nodes, clinical (N)	NX
N0		No regional lymph node metastasis
N1		Metastasis in movable ipsilateral axillary lymph node or nodes
N2		Metastasis in ipsilateral axillary lymph nodes or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a		Metastasis in ipsilateral axillary nodes fixed to one another (matted) or to other structures
N2b		Metastasis only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3		Metastasis in ipsilateral infraclavicular lymph node(s) or in clinically detected ipsilateral internal mammary lymph node or nodes and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node or nodes with or without axillary or internal mammary lymph node involvement
N3a		Metastasis in ipsilateral infraclavicular lymph node(s)
N3b		Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c		Metastasis in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (pN) [‡]	pNX	Regional lymph nodes cannot be assessed (e.g., previously removed)
	pN0	No regional lymph node metastasis histologically
	pN0(i–)	No regional lymph node metastasis histologically, negative IHC
	pN0(i+)	Malignant cells in regional lymph node(s) ≤ 0.2 mm (detected by IHC including isolated tumor cells)
	pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
	pN0(mol+)	No regional lymph node metastasis by IHC or histology, positive molecular findings (RT-PCR)
	pN1	Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically detected
	pN1mi	Micrometastases (> 0.2 mm, and/or > 200 cells, none > 2.0 mm)
	pN1mi	Micrometastases (> 0.2 mm and/or > 200 cells, but none > 2.0 mm)
	pN1a	Metastasis in one to three axillary lymph nodes, at least one metastasis > 2 mm
	pN1b	Metastasis in internal mammary nodes with micrometastases or macrometastases; microscopic disease detected by sentinel lymph node dissection but not clinically detected
	pN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node dissection but not clinically detected

Table 3 Continued

	pN2	Metastasis in four to nine lymph nodes or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastasis
	pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)
	pN2b	Metastasis in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastasis
	pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected, or in ipsilateral supraclavicular lymph nodes
	pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes
	pN3b	Metastasis in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
	pN3c	Metastasis in ipsilateral supraclavicular lymph nodes
Distant metastases (M)	MX	Distant metastasis cannot be assessed
	M0 cM0(+)	No clinical or radiographic evidence of distant metastases No clinical or radiographic evidence of distant metastases but deposits of molecularly or microscopically detected tumor cells in blood, bone marrow, or nonregional nodes ≤ 0.2 mm without symptoms or signs of metastases
	M1	Distant detectable metastases as determined by classic clinical and radiologic means and/or histologically proven > 0.2 mm

IHC = immunohistochemistry; RT-PCR = reverse transcriptase–polymerase chain reaction.

Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated as “sn” for sentinel node (e.g., pN0 (sn)).

Staging is the most important component in establishing prognosis. Indeed, axillary lymph node status and tumor size are the two most important determinants of outcome

Table 4 TNM Stage Grouping for Breast Cancer³⁸

Stage	T	N	M
0	Tis	N0	M0
1A	T1	N0	M0
1B	T0 or T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	
	T2	N0	
IIB	T2	N1	M0
	T3	N0	
IIIA	T0	N2	M0
	T1	N2	
	T2	N2	
	T3	N1 or N2	
IIIB	T4	Any N	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

for patients with early breast cancer. Other established factors that help define prognosis are estrogen receptor–alpha (ER), progesterone receptor (PR), and HER-2/neu/c-erb-B2 content of the primary tumor mass and histologic grade of the tumor. Biologic factors that are under evaluation for determining prognosis include other genes, such as *TP53* and *c-myc*, and various measures of cellular proliferation, such as S-phase fraction or Ki-67. Factors associated with poorer prognosis are lymph node involvement, increasing tumor size, high histologic grade, absence of ER and PR expression, and overexpression of HER-2. In addition, overexpression of other oncogenes, as well as increased cellular proliferative measures, may be associated with adverse clinical outcome. A newer area of research is predictive factors—that is, identification of biologic features correlated with sensitivity or resistance of a tumor to a particular therapy. There are three established predictive factors for breast cancer: ER, PR, and HER-2. The majority of tumors that express ER, PR, or both are initially sensitive to endocrine therapies, whereas tumors that lack ER and PR rarely respond to such treatment. Similarly, overexpression of the HER-2 protein or amplification of the *HER-2* gene is associated with response to the HER-2–targeted monoclonal antibody, trastuzumab or pertuzumab, or the small molecular inhibitor of HER-1 and HER-2, lapatinib. Much work continues on whether the overexpression of the HER-2 protein may be associated with sensitivity to certain chemotherapeutics or relative resistance to certain hormone therapies, such as tamoxifen.

Biologic and technical advances have permitted more complete interrogation of tumors by transcriptional profiling, leading to the delineation of at least four intrinsic subtypes of breast cancer—luminal A and B, HER-2–overexpressing, and basal breast cancers.³⁹ Whole exome or genome sequencing holds the promise of identification of even more subtypes. The development of multigene assays has ensued, and these are now entering clinical investigation and, in some cases, clinical practice. One such assay, OncotypeDx, may assist in the identification of women with axillary lymph node–negative, steroid receptor–positive breast cancer who would benefit from the addition of chemotherapy to tamoxifen.⁴⁰ A second assay, MammaPrint, is felt to have utility as a means of identifying young women with breast cancer associated with an especially poor prognosis.⁴¹ Several other assays are under development.³⁹ It is likely that genomic and proteomic profiling will become part of routine practice, but much remains to be done to establish the precise role of these types of assays.

Early Breast Cancer (Stages I and II)

DIAGNOSIS

Many cases of early, clinically occult breast cancer are diagnosed on the basis of architectural changes or microcalcification seen on a mammogram. Women with clinically evident breast cancer generally present with breast-specific complaints, such as a palpable mass, a change in breast contour, or skin or nipple changes. For both clinically occult and clinically apparent cancer, pathologic evaluation is mandatory to establish a diagnosis. In the past, incisional or excisional biopsies were routinely employed for this purpose. Today, fine-needle aspiration and core-needle biopsy are the standard diagnostic modalities. These procedures can be performed in the office in patients with suspicious palpable lesions. For women with nonpalpable lesions, biopsies guided by mammography, ultrasonography, or MRI are now routine. These technologies permit an accurate diagnosis, which can be followed by definitive treatment planning; consequently, only a single surgical procedure is required. Alternatively, women whose diagnoses are unequivocally negative can be spared an open surgical biopsy. However, it is axiomatic that further evaluation be undertaken for suspicious lesions that yield an equivocal diagnosis after needle aspiration or core biopsy. In addition, bilateral breast imaging is required to identify any unsuspected lesions in the contralateral breast that may also mandate further evaluation.

LOCAL TREATMENT OF EARLY-STAGE BREAST CANCER

In Situ Carcinoma

Because of increased use of screening mammography and heightened breast cancer awareness, in situ carcinomas now account for about 20% of newly diagnosed cases of breast cancer. The majority of these carcinomas are ductal carcinoma in situ (DCIS).⁴² Such lesions are associated with an approximately 30% risk of subsequent invasive breast cancer in the ipsilateral breast. The risk of metastatic breast cancer is small with DCIS; as a consequence, axillary lymph

node evaluation is not routinely performed. Thus, management decisions are centered largely on the involved breast. Total mastectomy, the traditional therapy, has a high likelihood of cure. Studies suggest that breast conservation is appropriate for many women with DCIS. Contraindications are poor cosmesis or multifocal disease. Several models using pathologic factors to predict outcome have been devised to guide decisions about local therapy; key factors are the size and grade of the lesion and the status of surgical margins. If breast conservation is the goal, then an adequate excision to obtain tumor-free margins is important. Careful mammographic examination of the specimen and postexcision mammography of the breast are crucial to ascertain whether the lesion has been fully excised. A meta-analysis of four randomized trials has demonstrated that radiotherapy along with lumpectomy, compared with lumpectomy alone, decreases the likelihood of recurrence of invasive or in situ breast cancer without an impact on survival.⁴³ Nonetheless, some women with favorable lesions who are willing to undergo close surveillance are candidates for local excision alone. An observational trial suggests that women with low or intermediate DCIS with negative margins can be managed with excision alone with an ipsilateral local failure rate of 10.5% at 7 years.⁴⁴ Randomized trials have also suggested value for the use of tamoxifen as a means to decrease both ipsilateral and contralateral disease. Evaluation of aromatase inhibitors as an alternative to tamoxifen for management of postmenopausal women with DCIS is in progress.

Controversy exists as to whether LCIS is truly a malignant lesion. Diagnosis of LCIS is usually an incidental finding on breast biopsy and appears to be associated with a 30% risk of development of invasive breast cancer in either breast. Women with LCIS are generally regarded as candidates for careful surveillance with regular breast examination and mammography. Bilateral total mastectomy may be considered for women with LCIS who have other risk factors or who are extremely concerned. The US breast cancer prevention trials suggested that a 5-year regimen of tamoxifen or raloxifene decreases the risk of invasive breast cancer by one half in women with LCIS; thus, these agents can also be considered for these women.^{19,20,26}

Invasive Breast Cancer

Surgical therapy Although radical mastectomy (removal of the involved breast, axillary contents, and underlying chest wall musculature) was the mainstay for breast cancer treatment for many decades, it is seldom performed today. Multiple randomized trials have uniformly and unequivocally shown that breast conservation therapy (BCT; lumpectomy with radiotherapy) and modified radical mastectomy (removal of the breast and axillary nodes) provide identical survival rates for women with stage I or II breast cancer.⁴⁵ Patient preference (rather than physician preference) should guide decision making regarding these two options. Medical contraindications for BCT are multifocal disease, ongoing pregnancy that precludes timely administration of radiotherapy, and previous radiotherapy. Although the number of patients being managed with BCT has risen substantially over the past 10 years, wide geographic differences exist in the use of this modality in the United States. Patients

who undergo mastectomy should be counseled about the availability of breast reconstruction alternatives.

Because the likelihood of distant micrometastatic spread is highly correlated with the number of involved lymph nodes, axillary dissection has traditionally been used to provide prognostic information about the extent of pathologic lymph node involvement. Therapeutic benefit from axillary dissection is minimal, and the morbidity associated with breast cancer surgery is largely related to side effects from axillary dissection. Unfortunately, use of prognostic factors derived from the primary tumor has not proved to be an acceptable alternative to assessment of axillary lymph node status. In recent years, sentinel lymph node mapping has become the method of choice to evaluate the ipsilateral axillary nodes.

Sentinel lymph node mapping involves injection of a radioactive tracer, vital blue dye, or both into the area around the primary breast tumor. The injected substance tracks rapidly to the dominant axillary lymph node(s)—the so-called sentinel lymph node(s). This node can be located by use of a small axillary incision and visual inspection or by use of a handheld counter. If the sentinel node is tumor free, the remaining lymph nodes are likely to be tumor free as well, and further axillary surgery can be avoided. Randomized trials have suggested similar outcomes for sentinel lymph node management versus standard axillary dissection, supporting the use of sentinel lymph node excision as the standard of care for most women with early-stage breast cancers.^{46,47} Another randomized trial has suggested that women in whom the sentinel node is found to contain a tumor need not always undergo lymph node dissection.⁴⁸ Sentinel node mapping is generally indicated only for women with invasive breast cancer without palpable axillary lymph nodes. Women with palpable nodes should undergo standard axillary dissection.

Adjuvant radiotherapy Radiotherapy is a critical component of BCT; a meta-analysis of nearly 11,000 women in 17 randomized trials of radiotherapy or not after breast-conserving surgery showed that radiotherapy reduced the 15-year absolute risk of recurrence by 16% and breast cancer mortality by 4%.⁴⁹ Attempts to identify women whose tumors are so favorable that radiotherapy can be safely withheld have suggested that elderly women with early-stage hormone receptor–positive disease might represent such a population.⁵⁰ Randomized trials of shorter courses of radiotherapy (accelerated or intraoperative) are quite promising.⁵¹ In addition, given that most in-breast recurrences occur adjacent to the excised tumor bed, the utility of partial breast radiotherapy to deliver radiation to a smaller field is under evaluation.

A continuing controversy concerns the value of postmastectomy radiotherapy. Once routine, this practice was largely abandoned because a number of randomized trials and a meta-analysis failed to show any benefit in survival from use of this practice. In these trials, the incidence of locoregional recurrence was reduced by 50 to 75%, although cardiac toxicity increased. As a result, postmastectomy radiotherapy was limited to women with extensive local disease, such as skin or chest wall invasion or extensive lymph node involvement. Interest in this field has been revived by

the publication of randomized trials of mastectomy with or without subsequent radiotherapy, as well as a meta-analysis suggesting a survival advantage for women with node-positive breast cancer who received radiation.⁵² Many radiation oncologists now recommend postmastectomy radiotherapy for women with more than three involved lymph nodes and discuss its use with women who have one to three positive lymph nodes. Skeptics have argued that the local recurrence rate in the women treated with mastectomy alone in these trials is higher than that observed in the United States today; thus, the seemingly positive results from the addition of radiotherapy may simply reflect salvage of patients who received inadequate surgery.

SYSTEMIC TREATMENT OF EARLY-STAGE BREAST CANCER

A driving force behind the use of systemic therapy for early-stage breast cancer has been the understanding that many women with primary breast cancer already have distant micrometastases at the time of diagnosis. Over time, overt metastatic disease develops in most of these women despite treatment with state-of-the-art surgery and radiotherapy. Thus, systemic therapy is frequently used in these women to prevent or delay recurrence of disease. The treatment algorithms that are currently in use are the result of over 50 years of clinical trials; the results of these trials have been compiled in sequential overview analyses that have evaluated the worldwide experience with use of ovarian ablation, tamoxifen therapy, and chemotherapy. The results of a recent meta-analysis for each modality of therapy are summarized and further updated below. In addition, a new class of agents, the aromatase inhibitors, has entered the adjuvant arena for postmenopausal women with steroid receptor–positive breast cancer.

Ovarian Ablation and Suppression

Ovarian ablation through surgery or radiotherapy is the oldest form of systemic therapy for advanced breast cancer. It was also the first adjuvant systemic therapy studied in a systematic fashion. More recent studies have focused on the use of luteinizing hormone–releasing hormone (LHRH) agonists as a means of effecting a temporary and reversible ovarian suppression. The efficacy of ovarian ablation or suppression was the subject of a 2000 meta-analysis that focused on about 8,000 women younger than 50 years who were participants in randomized trials begun before 1995.² Young age was used as a surrogate marker for premenopausal status. Some, but not all, of these studies involved chemotherapy. In these studies, positive hormone receptor status was generally not an entry criterion. Overall, these trials showed a significant reduction in the annual odds of recurrence and breast cancer mortality for women who underwent ovarian ablation in the absence of chemotherapy. The benefit was more modest for women treated with both ablation and chemotherapy. This finding is not surprising, because adjuvant chemotherapy can lead to the onset of menopause, and it is likely that the benefit of ovarian ablation or suppression is limited to women who are not menopausal. Benefits were enjoyed by both node-negative and node-positive women, but the absolute benefit was greatest in node-positive women who had a higher baseline risk of recurrence.

Interest in this general approach has been renewed by the advent of the LHRH agonists. These agents decrease the production of ovarian steroids through their effects on the hypothalamic-pituitary axis, in essence producing a temporary medical castration. Randomized trials in metastatic breast cancer patients suggest that these drugs, which include goserelin, leuprolide, and triptorelin, are as effective as oophorectomy. A meta-analysis of the trials addressing the efficacy of LHRH agonists in women with early-stage hormone-responsive breast cancer suggested the following: (1) LHRH agonist monotherapy has significant efficacy; (2) LHRH agonists appear to add benefit to adjuvant chemotherapy, especially in women younger than 40 years, who are less likely to be rendered menopausal by chemotherapy than older women are; and (3) the efficacy of LHRH monotherapy is similar to that of certain chemotherapy regimens.⁵³ In these trials, the regimens were given for 2 to 5 years. Unfortunately, these trials did not routinely employ tamoxifen, because its value in premenopausal women was generally recognized only after accrual for these studies had been completed. Nonetheless, the information on ovarian ablation and suppression suggests that in certain circumstances, ovarian ablation or suppression represents a viable adjuvant strategy for premenopausal women with steroid receptor-positive breast cancer.⁵⁴

Tamoxifen

The mixed estrogen agonist-antagonist tamoxifen has become the most commonly prescribed antineoplastic drug. After initial studies documented its efficacy in advanced breast cancer, a number of trials investigated its usefulness in women with early-stage breast cancer.² Information from most of the randomized trials of 5 years of tamoxifen is collected in the most recent overview analysis of tamoxifen, which included about 21,000 women from 20 trials.⁵⁵ This analysis confirmed that tamoxifen had minimal effect on outcome for women in whom expression of ER in their tumors was low or absent. These findings support preclinical and clinical data suggesting that tamoxifen's major mode of action is largely through its interaction with the ER. For those whose tumor expressed ER, the benefit of tamoxifen is unequivocal and persists with the passage of time. Indeed, in this patient population, the annual recurrence rate was nearly halved during the first 10 years after diagnosis, and breast cancer mortality was reduced by one third through the first 15 years after diagnosis. This corresponds to an absolute reduction of about 10% in both recurrence and breast cancer mortality after 15 years. Thus, benefit appeared to extend beyond the 5-year period of drug administration. The proportional reductions were similar for node-negative and node-positive women, but absolute improvements were greater in node-positive women. Benefit was observed regardless of age, menopausal status, tamoxifen dose, and use of chemotherapy. This overview also provided information on non-breast cancer outcomes, documenting a small increase in uterine cancer and a decrease in contralateral breast cancer. Use of tamoxifen had no effect on the incidence of other cancers or death from other causes.

Sequential trials have shown that a 5-year regimen of tamoxifen therapy gives better results than regimens of shorter duration. A recent study showed an advantage for

10 years of tamoxifen.⁵⁶ At least 5 years of tamoxifen is currently regarded as standard, while experts await the final results of a second large randomized trial of longer tamoxifen duration.

Aromatase Inhibitors

The aromatase inhibitors represent a good treatment strategy for postmenopausal women with steroid receptor-positive breast cancer.⁵⁷ In older women, the primary source of circulating estrogen is the conversion of androgens (synthesized by the adrenal glands) to estrogen via the action of the enzyme aromatase, which is found in certain tissues, including adipose and mammary tissues. The aromatase inhibitors specifically inhibit this conversion, leading to further estrogen deprivation in older women. Randomized trials have shown that the efficacy of aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) is similar or superior to that of tamoxifen and that aromatase inhibitors have an acceptable side-effect profile for postmenopausal women with metastatic breast cancer. Consequently, a series of randomized trials compared tamoxifen with an aromatase inhibitor as initial therapy and examined the value of either switching to an aromatase inhibitor after 2 to 3 years of tamoxifen therapy or adding an aromatase inhibitor after 5 years of tamoxifen therapy.⁵⁸⁻⁶² All of these strategies showed efficacy, leading to the recommendation that use of an aromatase inhibitor at some point should be considered for adjuvant therapy for most postmenopausal women with steroid receptor-positive invasive breast cancer.⁶³

Because information about long-term effects of aromatase inhibitors is still sparse, some experts have urged a cautious approach to their general use. Studies suggest that these agents are associated with postmenopausal symptoms, arthralgias, osteoporosis, and fractures. Unlike tamoxifen, aromatase inhibitors do not appear to be associated with uterine cancer risk or thromboembolic events. There is uncertainty about long-term side effects such as cardiac risk or effects on cognition. The optimal duration of aromatase inhibitor therapy is not known. The duration of treatment is often set at 5 years, by extrapolation from the tamoxifen experience.

No meaningful difference between the clinically available aromatase inhibitors has emerged to date. Given their mechanism of action, aromatase inhibitors should not be used in the treatment of premenopausal women.

Chemotherapy

The most recent chemotherapy overview assessed the benefit of polychemotherapy in 123 trials encompassing over 100,000 women.⁶⁴ This analysis addressed several general issues: polychemotherapy compared with no chemotherapy; anthracycline-containing regimens compared with the classic combination of cyclophosphamide, methotrexate, and fluorouracil (CMF); comparison of two different anthracycline-containing regimens; and taxane-containing versus non-taxane-containing regimens.

Other Chemotherapy Considerations

Selection of agents Initial studies of adjuvant chemotherapy used single agents such as melphalan. Because combination chemotherapy was found to effect higher response

rates in metastatic disease, the use of multiagent chemotherapy was introduced into the adjuvant setting. The landmark trial of Bonadonna and colleagues established CMF as a beneficial regimen for women with node-positive breast cancer.⁶⁵ The survival advantage of CMF persisted after 20 years of follow-up. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis confirmed that adjuvant chemotherapy reduces breast cancer mortality and overall mortality by about one third when compared with no adjuvant chemotherapy.⁶⁴ Given the efficacy of the anthracyclines (e.g., doxorubicin and epirubicin) in metastatic disease, combination regimens containing anthracyclines were also explored. The meta-analysis trials that compared CMF with combination regimens of cyclophosphamide, doxorubicin (Adriamycin) or epirubicin, and fluorouracil (CAF or FEC), as well as similar combination regimens, have shown that anthracycline provides a small benefit.² Selection of a regimen containing doxorubicin or epirubicin should be guided by patient and physician preference about relative toxicity and benefit.

Multiple trials in the meta-analysis have also evaluated the role of the taxanes (i.e., paclitaxel and docetaxel) in the context of anthracycline as adjuvant therapy.⁶⁴ In sum, these trials show that extending treatment through the addition of four cycles of taxane to a fixed anthracycline-control regimen reduced breast cancer mortality. However, no benefit was seen when the four cycles of taxane were compared with extra cycles of another cytotoxic regimen. A randomized comparison of docetaxel with paclitaxel and of weekly administration with administration every 3 weeks suggested that weekly paclitaxel was the most efficacious and least toxic in the adjuvant setting.⁶⁶ Some standard adjuvant chemotherapy regimens are described [see Table 5].

Duration Early adjuvant chemotherapy trials investigated therapies lasting up to 2 years. Sequential trials demonstrated that therapy lasting 2 years was no better than therapy lasting 1 year; subsequently, 6 months of therapy was found to be equivalent to 1 year of therapy. Moreover, longer treatment duration led to increased toxicity and decreased compliance. Other trials compared a single cycle of chemotherapy in the perioperative period with longer periods of administration and invariably showed improved outcome with prolonged therapy. Because of these trials, current adjuvant chemotherapy is generally administered for 3 to 6 months depending on the regimen chosen.²

Dose Preclinical data support the hypothesis that the chemotherapy dose is an important determinant of cell kill. As a consequence, the value of dose escalation has been studied extensively. Several trials now provide convincing evidence that reducing the dose to below a standard level is associated with an inferior outcome. In a pivotal trial addressing this issue, 1,550 women with node-positive breast cancer were randomly assigned to receive low, medium, or high doses of CAF.⁶⁷ Low-dose CAF was clearly associated with higher recurrence rates and poorer survival after follow-up of a median of 9 years. There was no difference in disease-free or overall survival between the moderate- and the high-dose arms. The high dose of CAF in this study is the same as the standard dose currently used in

adjuvant therapy. Preliminary studies suggest that the high-dose regimen was superior only in patients whose tumors had poor prognostic biologic factors.

Further dose escalation, made possible through the use of colony-stimulating factors, has not been beneficial. Three large randomized trials failed to show any value of either a fourfold increase in the dose of cyclophosphamide^{68,69} or a 50% increase in the dose of doxorubicin.⁷⁰ Thus, routine administration of high-dose chemotherapy is not warranted, because it can increase toxicity without improving outcome. In addition, a meta-analysis of randomized trials has shown that the administration of very high-dose chemotherapy combined with autologous bone marrow transplantation or peripheral progenitor cell support does not improve outcomes when compared with standard-dose therapy.⁷¹ Once popular for women with high-risk breast cancer, this approach has been largely abandoned. Regimens that use colony-stimulating factors to permit an accelerated schedule of chemotherapy administration have met with more success.⁷²

Timing Conventional adjuvant chemotherapy usually begins within a few months after surgery. Unnecessary delay is not advisable. Use of primary chemotherapy (i.e., chemotherapy administered before surgery or radiotherapy) has also been advanced and has been tested in several randomized trials. The combined results of these trials show that primary chemotherapy can increase the rate of breast conservation because of its ability to reduce tumor size.⁷³⁻⁷⁵ However, no reproducible advantage in other clinical outcomes has emerged. In the largest trial, about 1,500 women with palpable breast cancer were randomized to receive four cycles of doxorubicin and cyclophosphamide (AC) chemotherapy either before or after surgery.⁷³ After 5 years, disease-free survival and overall survival were identical for both groups. Therefore, primary chemotherapy is a safe alternative to traditional adjuvant chemotherapy, particularly for women who desire breast conservation and who are not considered appropriate candidates for breast-conserving surgery at the time of diagnosis. Studies are in progress to determine whether the response to primary chemotherapy can be used to guide further therapy and whether attainment of a pathologic complete response is a predictor of improved outcome.

Given the prevalence of BCT, a second issue concerns the timing of chemotherapy in relation to radiotherapy. A randomized trial compared the outcome of women treated with AC chemotherapy followed by breast radiotherapy with the outcome of women who received radiotherapy first, followed by identical AC chemotherapy.⁷⁶ This small trial did not show a clear difference between the two approaches. Other strategies include concomitant chemotherapy and radiotherapy and so-called sandwich therapy, in which several cycles of chemotherapy are administered, followed by radiotherapy and then the remaining cycles of chemotherapy. Concurrent chemotherapy and radiotherapy requires that certain drugs, such as doxorubicin and methotrexate, be omitted during the period of radiotherapy to prevent toxicity. The available data are not sufficient to definitively judge the effects of concurrent or sandwich therapy on long-term outcome.

Table 5 Some Commonly Used Adjuvant Chemotherapy Regimens

Acronym	Drugs	Dose	Schedule
CMF	Cyclophosphamide	100 mg/m ² /day p.o. × 14 days	Repeated every 28 days for six cycles
	Methotrexate	40 mg/m ² IV days 1 and 8	
	Fluorouracil	600 mg/m ² IV days 1 and 8	
CAF	Cyclophosphamide	100 mg/m ² /day p.o. × 14 days	Repeated every 28 days for six cycles
	Doxorubicin (Adriamycin)	30 mg/m ² IV days 1 and 8	
	Fluorouracil	500 mg/m ² IV days 1 and 8	
FAC	Fluorouracil	500 mg/m ² IV days 1 and 8	Repeated every 21 days for six cycles
	Doxorubicin	50 mg/m ² IV day 1	
	Cyclophosphamide	500 mg/m ² IV day 1	
AC	Doxorubicin	60 mg/m ² IV day 1	Repeated every 21 days for four cycles
	Cyclophosphamide	600 mg/m ² IV day 1	
AC → T	Doxorubicin	60 mg/m ² IV day 1	Repeated every 21 days for four cycles
	Cyclophosphamide followed by	600 mg/m ² IV day 1	
	Paclitaxel (Taxol)	175 mg/m ² IV day 1	
Dose-dense AC → T	Same as AC → T	Same as AC → T	Repeated every 14 days for four cycles with G-CSF support
AC → docetaxel	Doxorubicin	60 mg/m ² IV day 1	Repeated every 21 days for four cycles
	Cyclophosphamide followed by	600 mg/m ² IV day 1	
	Docetaxel	100 mg/m ² IV day 1	
TAC	Docetaxel (Taxotere)	75 mg/m ² IV day 1	Repeated every 21 days for six cycles
	Doxorubicin	50 mg/m ² IV day 1	
	Cyclophosphamide	500 mg/m ² IV day 1	
FEC	Fluorouracil	Various doses	Various schedules
	Epirubicin		
	Cyclophosphamide		
TC	Docetaxel	75 mg/m ² IV day 1	Repeated every 21 days for four cycles
	Cyclophosphamide	600 mg/m ² IV day 1	

G-CSF = granulocyte colony-stimulating factor.

Chemoendocrine Therapy

Chemotherapy and tamoxifen or aromatase inhibitor In light of the benefits of adjuvant chemotherapy and endocrine therapy when administered singly, a logical question concerns the role of combination therapy. Several pivotal trials have examined the value of chemotherapy combined with tamoxifen in node-positive and node-negative breast cancer. One such trial analyzed the value of tamoxifen alone, the combination of tamoxifen with CMF, and the combination of tamoxifen with methotrexate and fluorouracil (MF) for women with node-negative, steroid receptor-positive breast cancer.⁷⁷ Although reduced recurrence rates and improved survival rates were noted for all women who received combination therapy, the magnitude of the benefit of combination therapy was greatest in younger women or in those with larger tumors. The OncotypeDx assay (see above) was useful in identifying those women who benefited the most from chemotherapy.⁴⁰

The efficacy of chemotherapy in combination with tamoxifen for postmenopausal women with node-positive, steroid

receptor-positive breast cancer has been addressed.^{78,79} Several recent trials suggest that the addition of tamoxifen to chemotherapy reduces recurrence rates by 5 to 7% at 5 years, making the combination of chemotherapy and tamoxifen a reasonable choice for these women. Similarly, the addition of tamoxifen to chemotherapy for premenopausal women with node-positive, steroid receptor-positive breast cancer leads to a 10% improvement in 5-year recurrence-free survival.⁸⁰ Not surprisingly, the addition of tamoxifen to chemotherapy has not improved clinical outcome for women with steroid receptor-negative breast cancer in two randomized trials.^{81,82} Together, these trials suggest that chemohormonal therapy is a reasonable consideration for many women with steroid receptor-positive breast cancers. However, an explicit discussion of the magnitude of the potential benefits and side effects is critical because some women may find the benefit of combined therapy to be too small to warrant its toxicities. A 2006 analysis of chemotherapy benefits in women with ER-positive or ER-negative breast cancer enrolled in three randomized trials suggested that the

benefit of chemotherapy was greatest in women with ER-negative tumors.⁸³ In addition, the OncotypeDx assay (see above) may be useful in identifying those women with steroid receptor–positive node-negative breast cancer whose outcome is improved with the addition of chemotherapy to tamoxifen.

If chemotherapy and tamoxifen are both planned, a sequence of chemotherapy followed by tamoxifen is advisable. An Intergroup trial comparing the efficacy of combined CAF and tamoxifen with the efficacy of CAF followed by tamoxifen in postmenopausal women with node-positive, steroid receptor–positive breast cancer showed an advantage to the sequential approach.⁷⁹

No information is available concerning how to integrate chemotherapy with the use of an aromatase inhibitor. Extrapolating from the information on chemotherapy and tamoxifen, a prudent strategy is to use the sequence of chemotherapy followed by an aromatase inhibitor.

Chemotherapy and ovarian ablation The combination of chemotherapy and ovarian ablation has been assessed in trials using surgical oophorectomy or the administration of LHRH analogues for 2 to 5 years. One large trial showed no overall advantage after 9 years for CAF chemotherapy followed by 5 years of goserelin in 1,500 premenopausal women with node-positive, steroid receptor–positive breast cancer compared with CAF.⁸⁴ However, the LHRH agonist meta-analysis discussed earlier does suggest that a small benefit may be seen with the use of such agents after chemotherapy, especially in women under 40 years who are likely to remain premenopausal after adjuvant chemotherapy.⁵³ These trials are somewhat difficult to interpret because few of them used tamoxifen in a contemporary fashion.

Combination endocrine therapy Because different endocrine agents have different mechanisms of action, combination hormone therapy may have better results than either approach used alone. Indeed, combined endocrine therapy in metastatic breast cancer can increase the response rate, albeit with higher toxicity and generally without a superior effect on long-term outcome. In the adjuvant setting, ovarian ablation combined with tamoxifen or an aromatase inhibitor has been shown to be equally effective in premenopausal women. The combination of tamoxifen and anastrozole was shown to be no better than anastrozole alone in a large randomized trial in postmenopausal women.⁵⁸

Growth factor–targeted therapy Increased understanding of growth pathways of breast cancer has led to the identification of crucial nonendocrine pathways that are potential targets for therapy. One such target is the HER-2 protein, a transmembrane protein that is overexpressed in about 20% of breast cancers, generally because of gene amplification. Because of the success and safety of anti-HER-2 targeted therapy in the setting of advanced breast cancer (see below), several large adjuvant studies have assessed the utility of adding the monoclonal antibody trastuzumab to standard adjuvant chemotherapy regimens.^{85–87} These trials were directed largely toward women with node-positive breast cancer that overexpressed the HER-2 protein; in aggregate,

they showed that the addition of trastuzumab for 1 year reduced the risk of recurrence by about 50%. An increase in cardiac toxicity was noted, however, particularly with the use of anthracycline-containing regimens. As a result, use of trastuzumab is considered for many women with HER-2–positive breast cancers. Important questions remain regarding long-term benefits and risk, optimal duration of therapy, and the role of trastuzumab in the absence of chemotherapy. The additional role of two other HER-2 targeted agents, lapatinib and pertuzumab, is under study in large adjuvant clinical trials that are testing their use in place of or in addition to trastuzumab.

An important factor in the decision to use adjuvant therapy is an accurate assessment of the likelihood of breast cancer relapse and mortality with and without therapy. Several tools can help guide this discussion.⁸⁸ In addition, several groups have devised guidelines for the use of adjuvant therapy. Those from the 2011 St. Gallen Breast Cancer Conference, a gathering of international breast cancer experts, are outlined in Table 6.⁸⁹ Recommendations from the 2000 National Institutes of Health Consensus Conference⁹⁰ and an algorithm derived from an evidence- and expert opinion–based analysis from the National Cancer Center Network (NCCN) are also available.⁹¹ The NCCN comprises breast cancer experts from a consortium of cancer centers designated by the National Cancer Institute. These are guidelines, not mandates; they represent a framework for individualized patient counseling about prognosis and therapy. Finally, adjuvant therapy remains imperfect. Numerous clinical trials continue, and participation in clinical trials represents an excellent treatment choice for many patients.

Toxicity of Adjuvant Chemotherapy

Increased use of adjuvant chemotherapy and longer survival have led to concerns about toxicity.⁹² Acute side effects

Table 6 An Algorithm for Suggested Treatment for Patients with Operable Breast Cancer from the 2011 St. Gallen Consensus Conference⁸⁹

	<i>Pathologic Definition</i>	<i>Suggested Treatment</i>
Luminal A	ER and/or PR positive HER-2 negative Ki-67 low	Endocrine therapy
Luminal B	Luminal B HER-2 negative ER and/or PR positive HER-2 negative Ki-67 high Luminal B HER-2 positive ER and/or PR positive HER-2 overexpressed Any Ki-67	Endocrine therapy ± cytotoxic therapy Cytotoxic therapy + anti-HER-2 therapy + endocrine therapy
HER-2 overexpressing	HER-2 positive (nonluminal) HER-2 overexpressed ER and PR negative	Cytotoxic therapy + anti-HER-2 therapy
Basal-like	Triple negative ER and PR negative HER-2 negative	Cytotoxic therapy

ER = estrogen receptor; PR = progesterone receptor.

of therapy are nausea and vomiting, bone marrow suppression, and hair loss; all are reversible, and the first two may be mitigated by the judicious use of antiemetics and colony-stimulating factors, respectively. Induction of menopause is a common concern for younger women. Its likelihood is related to the type of chemotherapy and the age of the patient. CMF and similar regimens are more likely to induce permanent menopause than AC therapy. With either type of regimen, the incidence of menopause is greatest for women 40 years of age and older, the majority of whom will suffer a drug-induced menopause. Given its association with breast cancer, hormone replacement therapy is not generally recommended in breast cancer survivors. Doxorubicin-related cardiomyopathy is another long-term consequence; clinical evidence of congestive heart failure is noted in about 1% of women who receive doxorubicin-containing adjuvant chemotherapy at standard doses. Use of common adjuvant chemotherapy regimens results in a very small incidence of acute leukemia, but there is no evidence of increased incidence of other second tumors. Concerns about cognitive impairment are under investigation.

FOLLOW-UP OF EARLY BREAST CANCER SURVIVORS

Most women with breast cancer present with stage I or II breast cancer and receive appropriate local and systemic therapy. A critical issue is how longitudinal follow-up should be conducted in these patients. Two randomized trials have addressed this issue.^{93,94} Both compared a schedule of physician visits and regular laboratory testing (i.e., chest x-ray, bone scanning, and blood studies) with a program of physician visits and laboratory testing that was restricted to evaluation of symptoms. Together, they showed that routine laboratory screening did not enhance survival or quality of life when compared with a program of careful clinical examination with testing tailored for symptoms and physical findings. About 70% of metastases were first detected by the patients themselves, even in the group undergoing physician and laboratory evaluation every 3 months. On the basis of these and other studies, the American Society of Clinical Oncology has published evidence-based guidelines for follow-up of asymptomatic survivors of early-stage breast cancer.⁹⁵ These guidelines are summarized in Table 7.

Stage III Breast Cancer

Stage III breast cancer accounts for about 10% of all breast cancers; it is characterized by a primary tumor measuring more than 5 cm, neoplastic invasion of the skin or chest wall, or a fixed tumor or lymph nodes. Inflammatory breast cancer falls into this category. Inflammatory breast cancer has a clinical presentation of breast swelling, erythema, warmth, and a peau d'orange appearance (characterized by a dimpled appearance caused by tumor infiltration of intradermal lymphatics); it may or may not be associated with a mass. These lesions are associated with a high risk of recurrence of local disease and with distant metastases. Because as many as one third of women with clinical stage III breast cancer have metastases at the time of diagnosis, many oncologists perform a metastatic evaluation at that time, even in asymptomatic patients. Diagnosis is usually established by core-needle biopsy. Combined-modality therapy is

Table 7 Guidelines for Surveillance of Asymptomatic Early Breast Cancer Survivors from the American Society of Clinical Oncology⁹⁵

Recommended	Patient education about signs and symptoms of recurrence
	History and physical examination every 3–6 mo for first 3 yr, every 6–12 mo for next 2 yr, and annually thereafter
	Counseling about monthly breast self-examination
	Annual mammography
	Regular gynecologic follow-up
	Coordination of care between providers
Not recommended	Complete blood count
	Automated chemistry panel
	Tumor markers (e.g., CEA, CA 27-29, CA 15-3)
	Bone or PET scans
	Chest x-ray
	CT of chest, abdomen, pelvis or brain Liver ultrasound Breast MRI

CA = cancer antigen; CEA = carcinoembryonic antigen; CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

preferred for this stage of breast cancer. Several months of preoperative chemotherapy or hormone therapy result in partial tumor regression in most patients, thereby allowing mastectomy or breast-conserving surgery to be undertaken. Definitive surgery at the time of diagnosis should be avoided because of the high risk of subsequent chest wall recurrence. Postoperative radiotherapy is employed to enhance local control.

Some studies suggest that administration of further chemotherapy, hormone therapy, or both is then desirable. Multimodality therapy results in a 5-year disease-free survival rate of about 50%. Follow-up algorithms are similar to those recommended for women with stage I or II disease.

Stage IV or Metastatic Breast Cancer

Although seldom curable, advanced breast cancer is a highly treatable disease. Palliation or prevention of symptoms is the primary goal of treatment. The median survival after diagnosis of metastatic disease is about 2 years, although the range is great. Longitudinal studies have documented a few long-term survivors, most of whom were patients with indolent disease.⁹⁶ Several recent clinical trials have documented small improvements in survival with some of the newer therapies.

DIAGNOSIS

As noted, most women with advanced disease present with symptoms or abnormal physical findings. Common sites of relapse are bone, local soft tissues, lung, and liver. If metastasis is suspected, relevant imaging studies (e.g., nuclear medicine, CT scanning, or both) and routine hematologic and biochemical blood studies to assess the location

and severity of involvement are warranted. Because of the gravity of the diagnosis, pathologic confirmation is preferred. This permits verification of recurrent disease, exclusion of other diagnoses, such as a second primary cancer, and validation of molecular markers such as ER and HER-2 status that could warrant different therapy. Elevated levels of tumor markers, such as cancer antigen (CA) 27-29 or carcinoembryonic antigen (CEA), or the presence of circulating tumor cells is not pathognomonic of recurrent disease, although they may be useful adjuncts in the assessment of the effects of therapy.

TREATMENT

Unlike in early-stage breast cancer, the role of surgery in metastatic disease is limited. It may be appropriate in some cases, such as excision of a solitary chest wall nodule, removal of a solitary brain metastasis, or orthopedic stabilization to prevent or treat a long-bone fracture. Radiotherapy is a mainstay in the management of advanced disease. It may be used at any time during the disease course to treat localized disease, such as brain metastases or painful bony metastases. In the end, however, systemic treatment is the primary mode of management of disseminated disease. Guiding principles for selection of therapy include maximal palliation of symptoms, prevention of disease-related complications, and minimization of therapy-related toxicity. For achieving these goals, endocrine therapy is preferred wherever feasible. An algorithm for systemic treatment selection in stage IV breast cancer is presented [see Figure 1].

Endocrine Therapy

Factors that support the use of hormone therapy are the expression of hormone receptors, a long disease-free interval, nonvisceral disease, and the absence of symptoms. Over half of the women who meet these criteria respond to their initial course of endocrine therapy. This response lasts for 9 to 12 months on average; the length of response is a predictor of the likelihood of response to a second course of hormone therapy when the first choice fails. A second course of hormone therapy is less likely to be effective, and the duration of response is shorter; again, the period of response provides an indication of the response to a third course of endocrine therapy. In this way, some women can receive serial endocrine therapy with good disease control for several years.

Numerous types of hormone therapy are now available. Surgical therapy (with the exception of oophorectomy) and first-generation therapies, such as high-dose estrogen, progesterone, and aminoglutethimide therapy, have largely been supplanted by agents with specific mechanisms of action, such as SERMs, aromatase inhibitors, and LHRH agonists. Selection is usually made on the basis of efficacy, menopausal status, and toxicity. An algorithm for the selection of endocrine therapy is presented [see Figure 2]. Much work is focused on means to delay or circumvent hormone resistance. One such agent, everolimus, that targets the PI₃ kinase pathway is now approved for use in conjunction with exemestane for postmenopausal women with tumor refractory to a nonsteroidal aromatase inhibitor.⁹⁷

Several months of therapy are necessary before the efficacy of a newly introduced hormone regimen can be judged.

In addition, hormone-related tumor flare—a syndrome of worsening symptoms and an increase in the levels of tumor markers that occurs within the first weeks of treatment—may occur in a few patients. This paradoxical response is usually of short duration and should not be confused with disease progression.

Chemotherapy

Eventually, most women with advanced breast cancer experience hormone-refractory disease and become candidates for chemotherapy. Serial chemotherapy is again the rule. Patients receive two to four cycles of therapy and are then evaluated for evidence of disease stabilization or improvement. The duration of therapy is not fixed. Several trials have compared the strategy of continuing therapy until the time of disease progression with the strategy of employing several cycles of therapy followed by a cessation of therapy, with reintroduction of therapy at the time of disease progression.^{98,99} In aggregate, these studies have shown survival to be the same with these two approaches, but quality of life, as judged by the patients themselves, is sometimes better with continuing therapy. Thus, decisions about continuation or termination of a particular therapy are driven by patient and physician perception of side effects and benefits.

The scope of breast cancer chemotherapy has changed dramatically over the past few years, with the availability of new agents, such as paclitaxel, docetaxel, vinorelbine, capecitabine, gemcitabine, eribulin, ixabepilone, and carboplatin, and novel preparations of pegylated liposomal doxorubicin and nano-albumin-bound paclitaxel in addition to well-established agents such as cyclophosphamide, methotrexate, doxorubicin, and 5-fluorouracil. A list of newer agents available for the treatment of advanced breast cancer is provided in Table 8. All of these agents are active individually and in combination. There has been considerable debate about the value of combination therapy, compared with sequential single-agent therapy, for metastatic breast cancer. However, current international guidelines recommend sequential monotherapy as the preferred choice for most patients with metastatic breast cancer.¹⁰⁰ Use of combination chemotherapy should be reserved for individuals with rapidly progressive and highly symptomatic or life-threatening disease. As with hormone therapy, response rates and durations diminish with each successive change in therapy.

A difficult question is when to stop chemotherapy altogether. Although no fixed rules exist, many patients and physicians opt for a program of supportive care if two successive chemotherapy regimens fail to elicit a tumor response or to delay tumor progression. As with early-stage breast cancer, the approach of high-dose chemotherapy combined with autologous bone marrow transplantation or stem cell support has not shown benefit.¹⁰¹

Biology-Based Therapy

An increased understanding of the biology of breast cancer has resulted in the identification of agents against new targets for therapy. The first of these, approved by the FDA, was the monoclonal antibody trastuzumab (Herceptin), which is active against the transmembrane HER-2 protein.

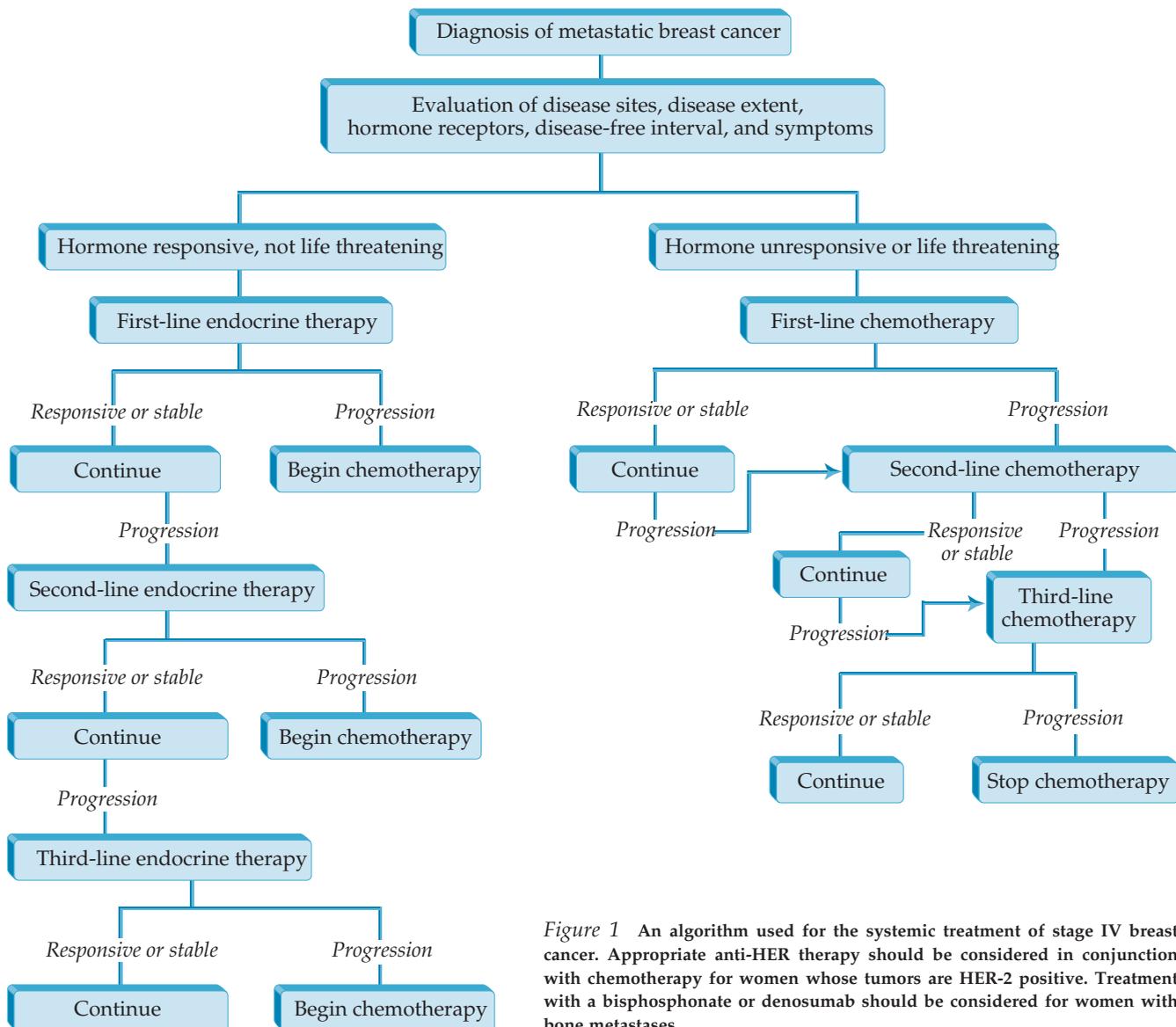


Figure 1 An algorithm used for the systemic treatment of stage IV breast cancer. Appropriate anti-HER therapy should be considered in conjunction with chemotherapy for women whose tumors are HER-2 positive. Treatment with a bisphosphonate or denosumab should be considered for women with bone metastases.

HER-2 protein is overexpressed in 20 to 30% of patients with breast cancers; such overexpression may be associated with poorer prognosis and resistance to certain therapies. Administration of trastuzumab to women whose tumor overexpressed HER-2 resulted in partial or complete tumor regression in 15% of heavily pretreated women and in more than 30% of untreated women.¹⁰² Concomitant administration of trastuzumab with certain cytotoxic agents has also been tested. In a randomized trial, concurrent treatment with trastuzumab and paclitaxel increased response rate, response duration, and survival, compared with paclitaxel alone, for women with newly diagnosed metastatic breast cancer.¹⁰³ Trastuzumab also enhanced the antitumor effects of AC chemotherapy, but the combination was associated with a 20% incidence of congestive heart failure. This unexpected finding highlights the need for careful evaluation of new biology-based therapies as they are introduced into clinical practice. The favorable risk-benefit ratio for trastu-

zumab in HER-2–overexpressing advanced breast cancer led to its successful translation into the adjuvant setting (see above).

Other molecular targets under investigation include the epidermal growth factor receptor or HER-1. Initial studies with gefitinib and erlotinib, small molecules that target the epidermal growth factor receptor tyrosinase kinase, in women with very advanced breast cancer showed little activity as monotherapy. However, a dual HER-1 and HER-2 receptor tyrosine kinase inhibitor, lapatinib, has been shown to enhance outcome for women with advanced breast cancer when added to capecitabine; further testing of its role in advanced and early-stage breast cancer is in progress.¹⁰⁴ The results to date suggest that, like trastuzumab, the benefit of lapatinib will be most marked in women whose tumors overexpress the HER-2 protein. A second monoclonal antibody, pertuzumab, has now entered clinical practice for use in conjunction with trastuzumab and taxane

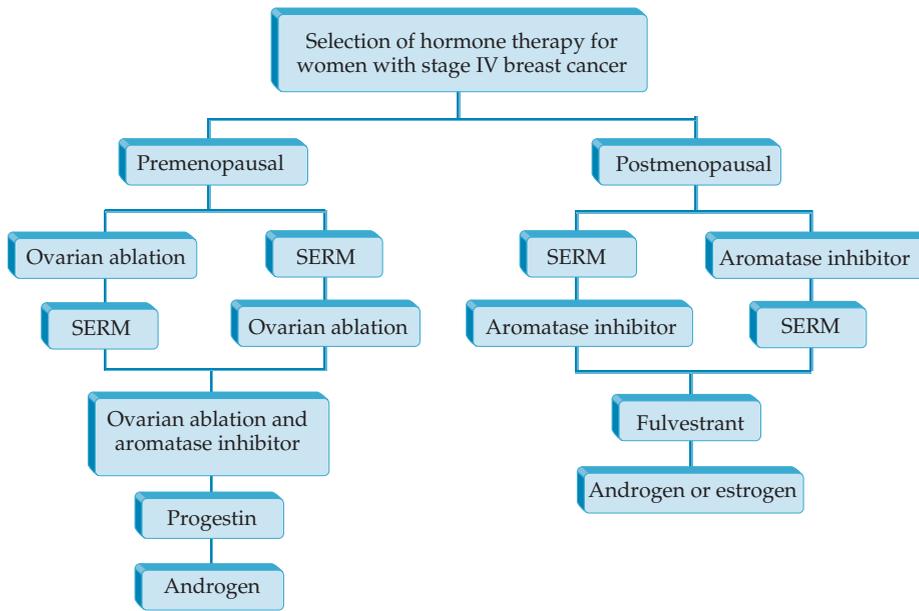


Figure 2 An algorithm used for hormone therapy for women with stage IV breast cancer. Concurrent treatment with a bisphosphonate or denosumab should be considered for women with bone metastases. SERM = selective estrogen receptor modulator.

for women with newly diagnosed HER-2-positive breast cancer.¹⁰⁵ Finally, the utility of a conjugate of trastuzumab with a cytotoxic agent has also been demonstrated.¹⁰⁶

Table 8 Some Newer Agents for Metastatic Breast Cancer Commercially Available in the United States

Drug	Category
Hormonal	
Toremifene (Fareston)	Selective estrogen receptor modulator
Anastrozole (Arimidex)	Aromatase inhibitor
Letrozole (Femara)	Aromatase inhibitor
Exemestane (Aromasin)	Aromatase inhibitor
Fulvestrant (Faslodex)	Selective estrogen receptor downregulator
Cytotoxic	
Docetaxel (Taxotere)	Taxane
Paclitaxel (Taxol)	Taxane
Vinorelbine (Navelbine)	Vinca alkaloid
Capecitabine (Xeloda)	Thymidylate synthase inhibitor
Gemcitabine (Gemzar)	Purine analogue
Ixapebilone (Ixemptra)	Nontaxane microtubule stabilizer
Eribulin (Halaven)	Nontaxane microtubule inhibitor
Biologic	
Trastuzumab (Herceptin)	Anti-HER-2
Lapatinib (Tykerb)	Anti-HER-1 and anti-HER-2
Pertuzumab (Perjeta)	HER-dimerization inhibitor
Everolimus (Afinitor)	Inhibitor of mammalian target of rapamycin (mTOR)
Bevacizumab (Avastin)	Anti-VEGF

VEGF = vascular endothelial growth factor.

Interventions that might block tumor angiogenesis are also under investigation. One such agent is bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor. This agent has modest activity as a single agent in advanced breast cancer, and its addition to chemotherapy has led to improvements in progression-free survival without a concomitant improvement in overall survival.¹⁰⁷ It is no longer approved for use in breast cancer by the FDA, and its use in conjunction with standard adjuvant and neoadjuvant approaches is under evaluation.

Supportive Care

Because palliation of symptoms and prevention of complications of disease are the primary goals of treatment of stage IV breast cancer, meticulous attention to supportive care is critical. Bone is the most common site of metastasis in breast cancer, and bony involvement can lead to significant morbidity. Several trials have demonstrated that regular administration of a bisphosphonate (zoledronate, pamidronate, or clodronate) or the RANK ligand inhibitor denosumab, in addition to hormone therapy or chemotherapy, can reduce pain and lower the incidence of several types of bony complications. Thus, the FDA has approved the use of zoledronate, pamidronate, or denosumab as adjunctive therapy for women with lytic bony metastasis from breast cancer. A number of issues remain unanswered, including the optimal treatment interval and duration of therapy. Several trials have tested the possibility that bisphosphonate may help prevent or delay the development of metastasis in women with early-stage breast cancer; the results of these randomized adjuvant trials are mixed. Currently, none of the agents are approved by the FDA as a form of adjuvant therapy for breast cancer, although they are frequently employed for management of bone health in breast cancer survivors. Evidence-based guidelines from the American Society of Clinical Oncology suggest that bisphosphonates be used only as part of a palliative program for women with metastatic bone disease.¹⁰⁸

Cardiotoxicity of doxorubicin may be reduced through the use of the cardioprotective agent dexrazoxane or liposomal preparations. Judicious application of colony-stimulating factors or erythropoietin may help diminish symptoms of chemotherapy-related bone marrow hypoplasia. Whether these strategies are superior to a reduction in chemotherapy dose or red blood cell transfusion remains to be determined. Adequate pain control should be achievable in most patients through the use of sustained-release oral and transdermal narcotic preparations. Excellent antiemetics, such as the serotonin receptor inhibitors (e.g., ondansetron) and a neurokinin-1 antagonist (aprepitant), are available to reduce chemotherapy-related emesis. Skillful application of these measures is critical in reducing morbidity from disease and its treatment.

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The drugs goserelin, leuprolide, and triptorelin have not been approved by the FDA for adjuvant uses described in this chapter. Bevacizumab has not been approved by the FDA for use in breast cancer. Exemestane has not been approved by the FDA for use in breast cancer risk reduction.

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