Clinical features, diagnosis, and staging of newly diagnosed breast cancer

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INTRODUCTION

Globally, breast cancer is the most frequently diagnosed malignancy, accounting for over two million cases each year [1]. It is also the leading cause of cancer death in women worldwide. In the United States, breast cancer is the most common female cancer, and the second most common cause of cancer death in women [2].

Once a diagnosis of breast cancer is established, it is important to accurately define the initial extent of disease since this information will affect treatment recommendations. This topic will review the clinical manifestations, differential diagnosis, and staging following a diagnosis of breast cancer.

The factors that modify breast cancer risk, the treatment approach to in situ and invasive breast cancer, and the use of prognostic and predictive factors when making adjuvant treatment decisions are reviewed as separate topics.

- (See "Factors that modify breast cancer risk in women".)
- (See "Ductal carcinoma in situ: Treatment and prognosis".)
- (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)
- (See "Overview of the approach to metastatic breast cancer".)

- (See "Prognostic and predictive factors in early, non-metastatic breast cancer".)

EPIDEMIOLOGY

Breast cancer is the most commonly diagnosed cancer worldwide, including low- and middle-income countries [3]. The incidence rates are highest in North America, Australia/New Zealand, and in western and northern Europe and lowest in Asia and sub-Saharan Africa [4]. These international differences are likely related to societal changes as a result of industrialization (eg, changes in fat intake, body weight, age at menarche, and/or lactation, and reproductive patterns such as fewer pregnancies and later age at first birth). Studies of migration patterns to the United States are consistent with the importance of cultural and/or environmental changes [5]. In general, incidence rates of breast cancer are greater in second-generation migrants and increase further in third- and fourth-generation migrants.

In the United States, breast cancer accounts for approximately 300,000 cases each year and is responsible for over 40,000 deaths [2]. The incidence rates decreased from 1999 to 2007 by 1.8 percent per year [6]. This decline in incidence reflects the end of the prevalence peak of screening. When women are screened for the first time, there is a "prevalence peak" that is due to cancers that have been building up in the population added to the cancers that are detected early due to the screening. An extended prevalence peak was seen with the gradual uptake of screening in the United States from the mid-1980s to 1999. The drop in incidence starting in 1999 reflected the end of the prevalence peak when participation in screening plateaued and, as expected, breast cancer incidence began to fall back to baseline. Discontinuation of hormone replacement therapy (HRT) had previously been touted as the major reason for this decline, although subsequent results from the Women's Health Initiative indicate HRT is safe in many postmenopausal women [7-12]. (See "Menopausal hormone therapy: Benefits and risks", section on 'Breast cancer'.)

Breast cancer mortality rates have been decreasing since the 1970s [13]. This decrease in mortality is due to improved breast cancer screening and improvements in adjuvant therapy [14,15]. Therapy saves lives when breast cancers are treated earlier, as demonstrated in a landmark article in which women age 40 to 69 years who participated in organized mammography screening had a 60 percent lower risk of dying from breast cancer within 10 years of diagnosis and a 47 percent lower risk of dying from breast cancer within 20 years of diagnosis compared with women who did not participate in screening [16].

Additional risk factors for breast cancer development and models to predict risk are reviewed separately. (See "Factors that modify breast cancer risk in women" and "Screening for breast cancer: Strategies and recommendations", section on 'Breast cancer risk determination'.)

CLINICAL FEATURES

The diagnosis of breast cancer requires histologic evaluation. The typical features of invasive breast cancer are reviewed below.

Signs and symptoms — In countries with established breast cancer screening programs, most patients present due to an abnormal mammogram. However, up to 15 percent of women are diagnosed with breast cancer due to the presence of a breast mass that is not detected on mammogram (mammographically occult disease), and another 30 percent present with a breast mass in the interval between mammograms (interval cancers) [17]. In addition, women without access to screening mammograms and younger women under 40 years who may not be undergoing routine screening mammograms may present with a breast or axillary mass with or without skin changes.

Breast mass — The "classic" characteristics of a cancerous lesion include a hard, immovable, single dominant lesion with irregular borders. However, these features cannot reliably distinguish a benign from a malignant tumor. (See "Clinical manifestations, differential diagnosis, and clinical evaluation of a palpable breast mass" and "Diagnostic evaluation of suspected breast cancer".)

Locally advanced disease — The signs of more advanced locoregional disease include axillary adenopathy (suggesting locoregional disease) or skin findings such as erythema, thickening, or dimpling of the overlying skin (peau d'orange), suggesting inflammatory breast cancer. (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer", section on 'Locally advanced breast cancer' and "Inflammatory breast cancer: Clinical features and treatment".)

Metastatic disease — Symptoms of metastatic breast cancer depend on the organs involved, with the most common sites of involvement being the bone (eg, back or leg pain), liver (abdominal pain, nausea, jaundice), and lungs (eg, shortness of breath or cough). (See "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Metastatic disease'.)

Imaging findings — Classic mammographic findings of breast cancer include the presence of a soft tissue mass or density (image 1) and suspicious microcalcifications. The most specific feature is a spiculated, high-density mass, with nearly 90 percent representing an invasive cancer. A more detailed discussion on the mammographic presentation of breast cancer is covered separately. (See "Diagnostic evaluation of suspected breast cancer", section on 'Mammographic features of breast cancer'.)

Breast ultrasound is often used to distinguish a benign versus malignant lesion. Sonographic features of malignancy include hypoechogenicity; internal calcifications; shadowing; a lesion

taller than it is wide; and spiculated, indistinct, or angular margins [18]. A typical ultrasound of early breast cancer is depicted here (image 2). (See "Diagnostic evaluation of suspected breast cancer", section on 'Ultrasonography'.)

Magnetic resonance imaging (MRI) is typically used to screen women at high risk for breast cancer. Although nearly all invasive breast cancers enhance on gadolinium contrast-enhanced MRI, MRI is not specific enough to obviate the need for biopsy. MRI features of breast cancer include irregular or spiculated mass margins, heterogeneous internal enhancement, and rim enhancement (image 3) [19]. Nonmass enhancement on contrast-enhanced MRI may also increase suspicion of an invasive lesion, particularly if the enhancement is associated with a mass or exhibits segmental distribution [19,20]. (See "MRI of the breast and emerging technologies", section on 'Screening high-risk women' and "Diagnostic evaluation of suspected breast cancer", section on 'Breast MRI'.)

DIAGNOSIS

The diagnosis of breast cancer is defined by the presence of malignant epithelial cells (carcinoma) on biopsy [21].

PATHOLOGY

There are various histologic types of breast carcinoma that differ in microscopic appearance and biologic behavior. (See "Pathology of breast cancer".)

The most common histologic types of epithelial breast carcinoma are described below.

Infiltrating ductal carcinoma — Infiltrating ductal carcinomas are the most common type of invasive breast cancer, accounting for 70 to 80 percent of invasive lesions. These lesions are characterized by cords and nests of cells with varying amounts of gland formation and cytologic features that range from bland to highly malignant.

Infiltrating lobular carcinoma — Infiltrating lobular carcinomas comprise about 8 percent of invasive breast cancers. Microscopically, they are characterized by small cells that insidiously infiltrate the mammary stroma and adipose tissue individually and in a single-file pattern.

Mixed ductal/lobular carcinoma — A mixed histologic appearance comprising both ductal and lobular characteristics is defined as a mixed invasive carcinoma. These comprise 7 percent of invasive breast cancers.

Other histologic types of breast cancer include metaplastic, mucinous, tubular, medullary, and papillary carcinomas. Together they account for less than 5 percent of invasive cancers. (See "Pathology of breast cancer".)

DIFFERENTIAL DIAGNOSIS

Breast cancers are heterogeneous in origin. The differential diagnosis of breast cancer includes malignancies that develop from epithelial, mesothelial, adenomyoepithelium, luminal progenitor, and basal stem cells [22].

The differential of a breast mass is reviewed separately. (See "Overview of benign breast diseases" and "Clinical manifestations, differential diagnosis, and clinical evaluation of a palpable breast mass" and "Atypia and lobular carcinoma in situ: High-risk lesions of the breast".)

For women who undergo a biopsy, the pathologic differential diagnosis must include other breast lesions beyond invasive breast cancer. Given the heterogeneity in the presentation and pathologic features of invasive breast cancer, expertise in breast pathology is often required to distinguish invasive carcinoma from other breast lesions. Breast lesions that should be considered in the review of pathology include:

- **Ductal carcinoma in situ (DCIS)** represents a heterogeneous spectrum of precancerous lesions confined to the breast ducts and lobules and is potentially a precursor lesion to invasive breast cancer. DCIS is characterized by the size of the lesion, nuclear grade, presence and extent of comedo necrosis, and architectural pattern. (See "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis".)

- **Microinvasive breast cancer** (or DCIS with microinvasion) typically presents as a palpable mass. On pathologic examination, it is an invasive carcinoma of the breast where the largest focus is no more than 1 mm. It tends to be associated with high-grade DCIS and comedo-type necrosis. (See "Microinvasive breast carcinoma".)

- **Other cancers –** The breast can give rise to other invasive malignancies separate from primary breast cancer. These rare tumors include sarcoma, Paget disease, malignant phyllodes tumor, and lymphoma. A biopsy is required to distinguish these tumors from primary breast cancer.

    - Breast sarcoma – Breast sarcomas are rare, histologically homogenous tumors that arise from the connective tissue within the breast. They can arise de novo, following radiation therapy, or in the context of lymphedema. (See "Breast sarcoma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging".)

- Paget disease – Paget disease of the breast typically presents as a raw, scaly, vesicular, or ulcerated lesion that begins on the nipple and spreads to the areola. Over 80 percent of cases are associated with an underlying breast cancer and are usually human epidermal growth factor 2 positive. (See "Paget disease of the breast (PDB)".)

- Phyllodes tumors – Phyllodes tumors are uncommon fibroepithelial breast tumors that can behave in variable fashion and are classified as benign, borderline, or malignant based on histologic criteria (cellular atypia, mitotic activity, margins, and stromal overgrowth). (See "Phyllodes tumors of the breast".)

- Lymphoma – Lymphoma of the breast typically presents as a painless unilateral breast mass in an older woman. The vast majority are non-Hodgkin lymphomas, most commonly of B-cell lineage. (See "Overview of the pathobiology of the non-Hodgkin lymphomas", section on 'B cell lymphoma'.)

POSTDIAGNOSIS EVALUATION

If cancer is identified, hormone receptor status is determined. (See 'Breast cancer receptor testing' below.)

In addition, patients should proceed with an appropriate staging work-up to determine local and distant extent of disease. Women presenting with signs or symptoms of metastatic breast cancer should undergo additional imaging; in addition, a biopsy should be done of at least one metastatic lesion to confirm the diagnosis of metastatic breast cancer. (See 'Role of imaging' below and 'Staging' below and 'Assessing the extent of local disease' below.)

Breast cancer receptor testing — Newly diagnosed breast cancers must be tested for estrogen (ER) and progesterone (PR) receptor expression and for overexpression of human epidermal growth factor 2 (HER2) receptors. This information is critical for both prognostic and therapeutic purposes. (See "Prognostic and predictive factors in early, non-metastatic breast cancer" and "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)

ER and PR — Estrogen receptor (ER) and progesterone receptor (PR) are prognostic factors for invasive breast cancer. In addition, patients with cancers that are ER and/or PR positive are treated with adjuvant endocrine therapy. ER-positivity is defined by immunohistochemistry (IHC) for ER and PR in more than 1 percent of tumor cells. More discussion on the use of ER/PR in breast cancer is covered separately. (See "Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy" and "Prognostic and predictive factors in early, non-metastatic breast cancer".)

HER2 — Human epidermal growth factor receptor 2 (HER2) overexpression is present in 15 to 20 percent of patients and predicts those who will benefit from HER2-directed therapy. HER2 overexpression is detected by uniform intense membrane staining of >10 percent of invasive tumor cells (IHC 3+) or the presence of HER2 gene amplification by fluorescence in situ hybridization defined as a ratio of HER2/CEP17 (centromeric probe to chromosome 17) ratio ≥2.0, with the *HER2* copy number signals/cell being ≥4. Other criteria for defining HER2-positivity also exist and are discussed elsewhere. (See "HER2 and predicting response to therapy in breast cancer", section on 'Testing for HER2 expression' and "Prognostic and predictive factors in early, non-metastatic breast cancer".)

Frequency of subtypes — Breast cancer can be characterized into different subtypes by whether or not they express ER, PR, and HER2 [23,24]. The proportions of breast cancers with different receptor phenotypes were evaluated in one study of 61,309 cases diagnosed between 1999 and 2004 [23]:

- Hormone receptor (ER and/or PR) positive cancers comprised the majority of cases (n = 48,851 cases, 80 percent).
- HER2 was overexpressed in 23 percent (n = 13,921). Of these, 67 and 32 percent were hormone receptor-positive and negative, respectively.
- ER, PR, and HER2-negative (triple negative) cancers comprised 13 percent (n = 8022).

However, the frequency of subtypes also varies according to race. As an example, in the Carolina Breast Cancer Study, compared with White American women (n = 631), African American women (n = 518) were less likely to have hormone receptor (ER/PR)-positive, HER2-negative disease (48 versus 64 percent, respectively) and more likely to have ER/PR/HER2-negative disease (22 versus 11 percent, respectively) [24].

Role of imaging — Our approach to imaging is as follows.

- Most patients with asymptomatic stage 1 or 2 cancers do not require imaging beyond the breast. (See 'Assessing the extent of local disease' below.)

For women with newly diagnosed breast cancer, we reserve imaging to evaluate for advanced or metastatic disease in the following situations:

- For patients with localized bone pain or an elevated alkaline phosphatase, we obtain a bone scan. If the bone scan is negative and clinical suspicion warrants further evaluation, magnetic resonance imaging (MRI) should be performed localized to the symptomatic area.
- For patients with abnormal liver function tests, an elevated alkaline phosphatase, abdominal pain, or an abnormal abdominal or pelvic examination, we obtain a

computed tomography (CT) scan of the abdomen and pelvis. Abdominal MRI or ultrasound would be reasonable alternatives depending on the specific symptom to be evaluated. Positron emission tomography-CT (PET-CT) would be reasonable if whole-body screening for metastatic disease is also desired.

- For patients presenting with pulmonary complaints (ie, cough or hemoptysis), we obtain a chest CT scan, although chest radiograph would be a reasonable alternative.

- For patients with stage IIIA or higher disease, regardless of whether symptoms are present or not, we obtain a whole-body PET-CT or, alternatively, a bone scan as well as a CT scan of the chest, abdomen, and pelvis (CT C/A/P). Patients with inflammatory breast cancer, regardless of stage, should also undergo imaging evaluation. (See "Inflammatory breast cancer: Clinical features and treatment", section on 'Staging and pretreatment evaluation'.)

  - In a randomized trial in 369 patients with stage III or IIb (T3N0, but not T2N1) breast cancer, 23 percent of patients assigned to staging with PET-CT were upstaged to stage IV compared with 11 percent assigned to conventional staging with CT C/A/P and bone scan (absolute difference, 12.3 percent [95% CI 3.9-19.9]) [25]. As such, fewer patients in the PET-CT group received combined modality therapy (81 versus 89 percent, absolute difference 8.2 [95% CI 0.1-15.4]).

  - A novel PET methodology, using fluoroestradiol F-18 as the radioactive diagnostic agent, is approved by the US Food and Drug Administration for the detection of ER-positive lesions, as an adjunct to biopsy, in patients with recurrent or metastatic breast cancer [26]. However, it does not as yet have a defined role in routine management of assessment of early breast cancer. This agent is being evaluated in clinical trials to determine clinical utility for predicting endocrine therapy response and to provide prognostic information [27-29]. (See "MRI of the breast and emerging technologies", section on 'Positron emission tomography scanning'.)

This approach is consistent with National Comprehensive Cancer Network guidelines [30] and is based on multiple studies that have shown extensive imaging has little yield for most patients with newly diagnosed breast cancer [31-33]. In one of the largest reports, 516 consecutive patients seen at one institution for newly diagnosed breast cancer were retrospectively evaluated to determine the impact of staging [33]. Major findings were:

- A bone scan detected bony metastases in 26 of 412 patients (6 percent). The prevalence of a positive bone scan for women with preimaging stage I, II, and III breast cancer was 5, 6, and 14 percent, respectively.

- Liver ultrasound detected hepatic metastases in 3 of 412 patients (0.7 percent). No patients with stage I or II breast cancer had liver metastases. For patients with stage III

breast cancer, the prevalence of a positive liver ultrasound was 6 percent.

- Chest radiograph detected lung metastases in 4 of 428 patients (0.9 percent). No patients with stage I or II breast cancer had pulmonary metastases. The prevalence of a positive chest radiograph among women with stage III disease was 7 percent.

Assessing the extent of local disease — Mammographic assessment of the extent of ductal carcinoma in situ (DCIS) and early invasive carcinoma begins during diagnostic mammography and continues through the biopsy, specimen management, and the postexcision mammogram [34]. Mammography of both breasts is particularly important in the patient with DCIS or invasive cancer who is considering breast conservation. Preoperative diagnostic mammography can help to define the extent of disease and may identify multifocal or multicentric cancer that could preclude breast conservation or signal a potential difficulty in achieving clear surgical margins. Multifocal disease is usually defined as involvement of several areas within a breast quadrant, probably representing disease along an entire duct. By contrast, multicentric disease involves multiple areas within different quadrants, probably representing involvement of multiple ducts.

Although the extent of mammographic nonlinear branching microcalcifications frequently underestimates the pathologic extent of the malignancy, the discrepancy is less than 2 cm in 80 to 85 percent of cases [35]. Several groups of microcalcifications separated by normal-appearing tissue should not be interpreted as multifocal or multicentric disease. Often, these represent areas of contiguous tumor that is only partially calcified within a ductal lobule [35,36].

The combination of a mass and associated calcifications often indicates the presence of an extensive intraductal component (EIC). EIC is defined pathologically as DCIS found adjacent to an invasive carcinoma, accounting for more than 25 percent of the volume of disease. This finding can be a predictor for more widespread residual tumor (usually DCIS) following gross excision of the lesion [37]. (See "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis".)

Postoperative mammograms to look for residual calcifications after surgical resection should be considered when the microcalcifications are not clearly or completely documented on the specimen radiograph, or when margins are close or positive [38,39]. If a re-excision is to be recommended based on residual calcifications, care should be taken to ensure that the calcifications are associated with malignancy on histopathology and not benign tissue. Multifocal disease is not necessarily a contraindication to breast conservation but is one of the factors that should be taken into consideration along with breast size relative to the extent of disease on imaging. (See "Breast-conserving therapy" and "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis".)

A significant limitation of mammographic assessment of disease extent is the obscuring of the borders or extent of the primary tumor by dense overlying tissue. Dense breasts can limit the sensitivity of mammography both for detection of breast cancers and for delineating disease extent [40-42]. In this setting, contrast-enhanced breast MRI may complement mammographic staging. If the clinical extent of disease is larger than what can be appreciated by mammography, MRI may be considered. (See "Diagnostic evaluation of suspected breast cancer", section on 'Breast MRI'.)

Contrast enhanced mammography is a new technology that approaches accuracy of MRI for pre-operative staging and may be considered in patients unable to obtain breast MRI [43].

Mammographic assessment of tumor size for the staging of multifocal disease presents a unique dilemma. Most staging classifications require that the largest tumor mass be utilized for T staging, even in cases where multifocal disease is suspected. However, others suggest that the total surface area, volume, or aggregate measurements are a better indicator of prognosis [44-46]. Accurate delineation of the extent of odd-shaped, irregular, or multifocal tumors is important for treatment planning. (See "Tumor, node, metastasis (TNM) staging classification for breast cancer".)

For invasive cancers that are contiguous to the chest wall and not completely included on mammographic projections, ancillary imaging techniques such as MRI may be necessary to assess posterior tumor extension and pectoralis fascia or muscle involvement if that will determine a change in surgical approach or the use of neoadjuvant therapy [47]. Breast MRI may also be useful for evaluating response to neoadjuvant therapy in locally advanced breast cancers and can provide prognostic information. In a multicenter trial of neoadjuvant chemotherapy, functional tumor volume at MRI was a stronger predictor of recurrence-free survival than pathologic complete response [48]. (See "General principles of neoadjuvant management of breast cancer", section on 'Clinical assessment and indications for imaging'.)

Significance of intramammary lymph nodes — Intramammary lymph nodes are detected in 1 to 28 percent of patients with breast cancer [49-53]. Benign nodes can often be distinguished from metastatic or infiltrated intramammary lymph nodes by their mammographic or sonographic appearance, but definitive assessment often requires histopathologic study [54]. The presence of intramammary lymph node metastases appears to confer a worse prognosis, both in women who otherwise have stage I breast cancer based upon tumor size and axillary nodal status and in those with higher stage disease [49]. Isolated clinically detected intramammary lymph node metastases are considered to represent stage III disease, even if the axillary nodes are uninvolved. (See "Tumor, node, metastasis (TNM) staging classification for breast cancer".)

GENETIC COUNSELING

Some patients with a diagnosis of breast cancer may be appropriate candidates for genetic evaluation to determine their own and family members' risk for future breast cancers and other malignancies. This is discussed in detail elsewhere. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes", section on 'Criteria for genetic risk evaluation'.)

In addition, patients with triple-negative breast cancer (at any age) or those with high-risk disease who would be candidates for adjuvant olaparib if they were found to have a *BRCA* mutation should be offered genetic counseling and testing. Criteria for adjuvant olaparib among *BRCA* carriers with high-risk early breast cancer are discussed elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Patient selection for adjuvant PARP inhibitors' and "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

STAGING

Breast cancer is staged using the American Joint Committee on Cancer and the International Union for Cancer Control classification system for Tumor, Nodes, and Metastases (TNM). The eighth edition of the TNM staging system, which was effective as of January 1, 2018, includes anatomic stage groups (table 1) as well as prognostic stage groups, which incorporate biomarker testing (table 2 and table 3). (See "Tumor, node, metastasis (TNM) staging classification for breast cancer".)

In the TNM system, patients are assigned a clinical stage (cTNM) preoperatively. Following surgery, the pathologic stage (pTNM) is then determined. For patients who undergo neoadjuvant treatment, the final pathologic stage is designated by the letter y (ypTNM). (See "Diagnostic evaluation of suspected breast cancer" and "General principles of neoadjuvant management of breast cancer", section on 'Pathologic assessment'.)

Primary tumor — Clinical tumor (T) stage is assessed by clinical examination and/or imaging. While the majority of breast cancers are associated with abnormal mammographic findings, breast ultrasound and/or magnetic resonance imaging may be required to accurately assess tumor size, particularly in patients presenting with a breast mass that is not identified on mammography. (See "Diagnostic evaluation of suspected breast cancer", section on 'Mammography and digital breast tomosynthesis' and "Diagnostic evaluation of suspected breast cancer", section on 'Ultrasonography' and "Diagnostic evaluation of suspected breast cancer", section on 'Breast MRI'.)

Lymph nodes — The status of the regional lymph nodes is one of the most important prognostic factors in early-stage breast cancer. Physical examination is neither a sensitive nor a reliable method to ascertain the status of the axillary lymph nodes because metastatic

lymph nodes are often not palpable and reactive lymph nodes may be mistaken for metastases. The positive predictive value of clinical palpation ranges from 61 to 84 percent, while the negative predictive value is only 50 to 60 percent [55-57].

Given these findings, axillary staging should be performed. The assessment and management of the regional lymph nodes in breast cancer are discussed separately. (See "Overview of management of the regional lymph nodes in breast cancer".)

Metastases — Most patients presenting with breast cancer have disease confined to the breast (stage I to II) with no or limited (ie, less than three) nodes involved. We do not routinely stage such patients in the absence of signs or symptoms suspicious for metastatic disease. We restrict further work-up to patients who present with locally advanced (T3 or greater, N2 or N3, M0) or inflammatory breast cancer and those with signs or symptoms suspicious for metastatic disease. Specific indications for imaging are discussed above. (See 'Role of imaging' above.)

Management of patients with metastatic disease is discussed above. (See "Overview of the approach to metastatic breast cancer" and "Epidemiology, clinical presentation, and diagnosis of bone metastasis in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Breast cancer (The Basics)")

- Beyond the Basics topics (see "Patient education: Breast cancer guide to diagnosis and treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Introduction –** Breast cancer is the most common malignancy diagnosed worldwide. Breast cancer mortality rates have been decreasing due to improved breast cancer screening and improvements in adjuvant therapy. (See 'Epidemiology' above.)

- **Presentation –** In countries with established breast cancer screening programs, most patients present due to an abnormal mammogram. However, women with advanced cases of breast cancer may present with skin changes (also known as peau d'orange) or axillary adenopathy. Less than 5 percent of patients present with signs or symptoms of metastatic breast cancer. (See 'Signs and symptoms' above.)

- **Evaluation**

  - Women who present with abnormal imaging findings alone should undergo biopsy guided by mammogram (stereotactic biopsy), ultrasound, or breast magnetic resonance imaging. (See "Breast biopsy".)

  - Women presenting with a suspicious palpable breast mass should undergo diagnostic imaging evaluation followed by a fine needle aspiration or core needle biopsy. (See "Breast biopsy", section on 'Core needle biopsy' and "Breast biopsy", section on 'Fine needle aspiration'.)

  - In addition to a biopsy of the breast, women presenting with signs of inflammatory breast cancer (eg, rapidly progressing, tender, firm, and enlarged breast with thickening of the underlying skin) require full-thickness skin biopsies. The presence of dermal lymphatic invasion is pathognomonic for inflammatory breast cancer. (See "Breast biopsy", section on 'Skin punch biopsy'.)

- **Diagnosis and pathology**

  - The diagnosis of breast cancer is defined by the presence of malignant epithelial cells (carcinoma) showing evidence of stromal invasion. (See 'Diagnosis' above.)

  - Most breast malignancies are carcinomas that arise from epithelial elements. However, there are various histologic types of breast carcinomas, such as sarcomas, that differ in microscopic appearance and biologic behavior. (See 'Differential diagnosis' above.)

- **Classification**

- Breast cancer can be categorized based on expression of estrogen (ER), progesterone, and human epidermal growth factor (HER2) receptors. Each of these factors influence prognosis for patients with invasive breast cancer and is used to individualize treatment options. (See 'Pathology' above and 'Postdiagnosis evaluation' above.)

- **Staging** – Breast cancer is classified according to the American Joint Committee on Cancer and the International Union for Cancer Control for tumor, nodes, and metastases (TNM; (table 1 and table 2 and table 3)). In the TNM system, patients are assigned a clinical stage (cTNM) preoperatively. Following surgery, the pathologic stage (pTNM) can be assigned. For patients who undergo neoadjuvant treatment, the final pathologic stage is designated by the letter y (ypTNM). (See 'Staging' above.)

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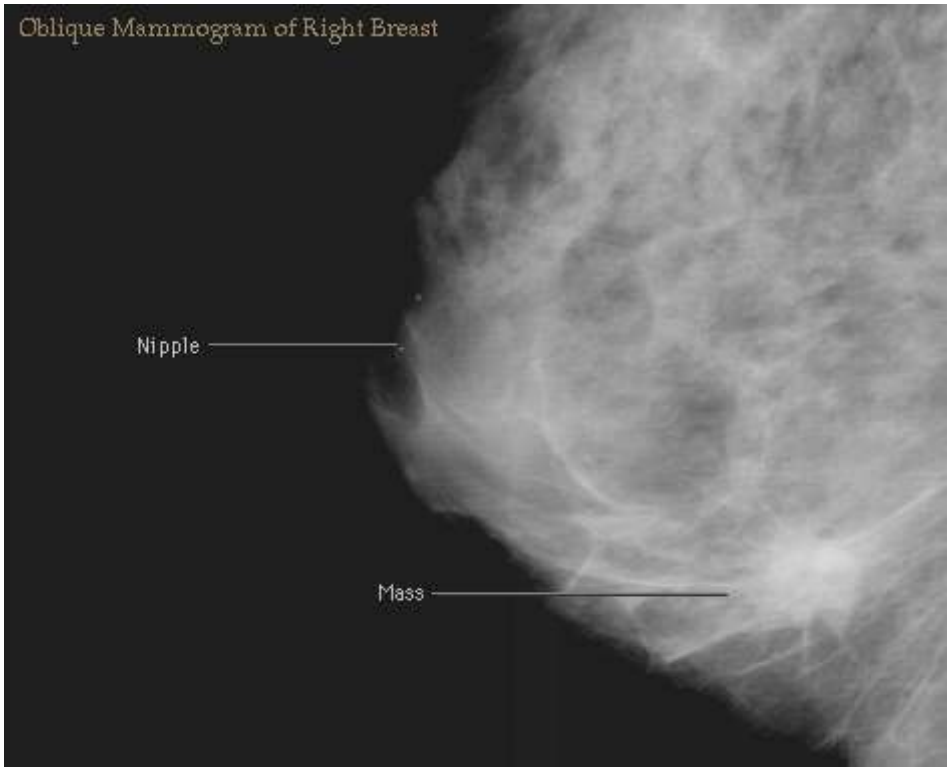
Topic 744 Version 60.0

GRAPHICS

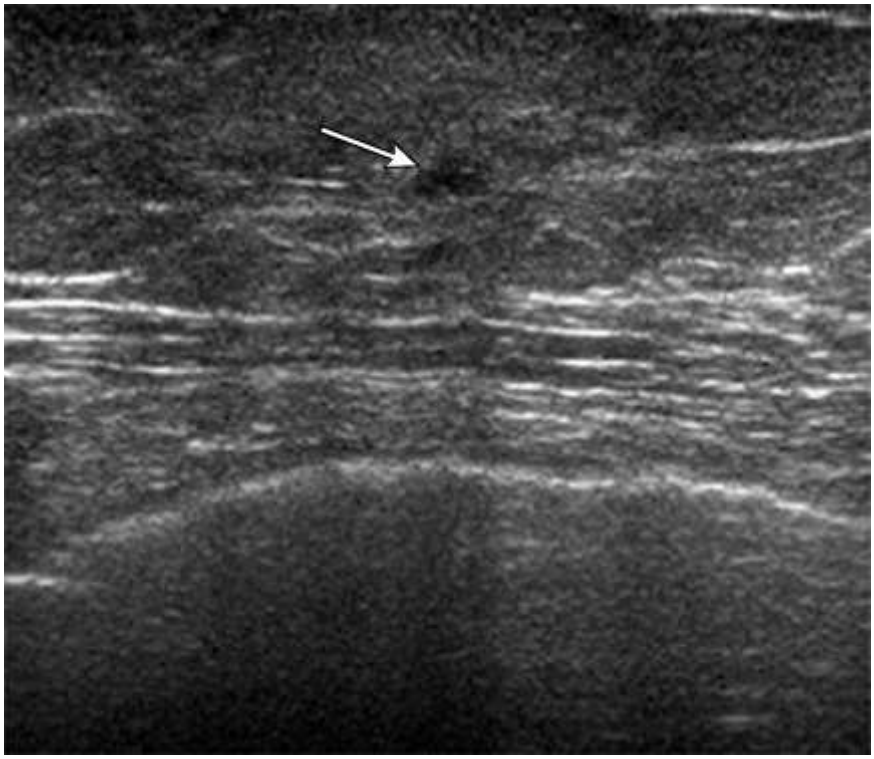
Abnormal mammogram



This is an abnormal mammogram showing a mass, caused by breast cancer.

Graphic 59883 Version 2.0

Ultrasound of early breast cancer

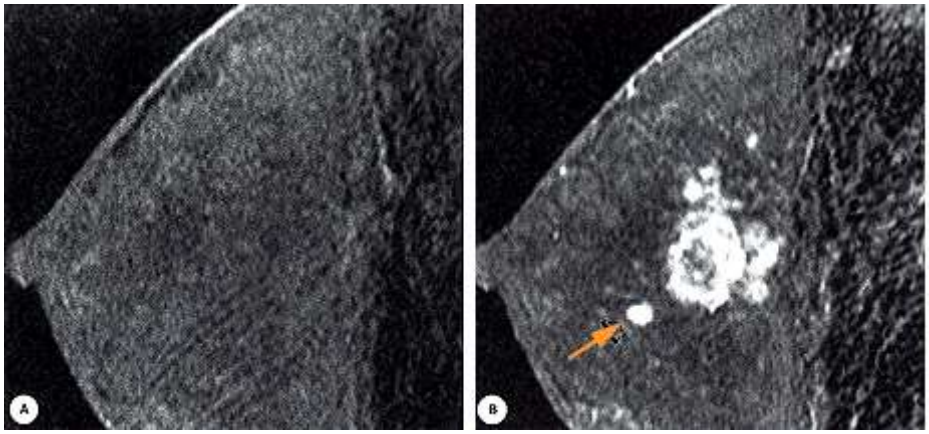


Left breast ultrasound shows a small breast cancer (arrow), a hypoechoic mass with posterior acoustic shadowing.

Courtesy of Pierre J Sasson, MD.

Graphic 52790 Version 5.0

Breast MRI



Staging breast magnetic resonance image (MRI) for invasive carcinoma poorly assessed on mammography. (A) Preconstrast 3-D FSPGR MRI image with fat suppression. (B) Postcontrast MRI delineates the extent of the invasive carcinoma as well as several clinically and mammographically occult satelite lesions (arrow).

Graphic 51605 Version 2.0

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110848 Version 8.0

Breast carcinoma TNM clinical prognostic stage groups AJCC UICC 8th edition

When TNM is…	And grade is…	And HER2 status is…	And ER status is…	And PR status is…	Then the clinical prognostic stage group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB

T0 N1[¶] M0 T1* N1[¶] M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T0 N1[¶] M0 T1* N1[¶] M0 T2 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
T0 N1[¶] M0 T1* N1[¶] M0 T2 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1[Δ] M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1[Δ] M0	G2	Positive	Positive	Positive	IB

T3 N0 M0				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
T2 N1[Δ] M0 T3 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0	G3	Positive	Positive	Positive	IIB
				Negative	IIIA

T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

NOTES:

1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with the clinical prognostic staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (eg, T0 N1, etc) or with breast ductal carcinoma *in situ* (eg, Tis N1, etc), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the clinical prognostic stage group table.
4. The prognostic value of these prognostic stage groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* T1 includes T1mi.

¶ N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Δ N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

Graphic 110851 Version 11.0

Breast carcinoma TNM pathologic prognostic stage groups AJCC UICC 8th edition

When TNM is…	And grade is…	And HER2 status is…	And ER status is…	And PR status is…	Then the pathological prognostic stage group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T0 N1¶ M0	G1	Positive	Positive	Positive	IA
				Negative	IB

T1* N1¶ M0 T2 N0 M0			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
T2 N1Δ M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1Δ M0 T3 N0 M0	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
T2 N1[Δ] M0 T3 N0 M0	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1[Δ] M0 T3 N2 M0	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA

			Negative	Positive	IIIA
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
T4 N0 M0 T4 N1[Δ] M0 T4 N2 M0 Any T N3 M0	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC
Any T Any N M1	Any	Any	Any	Any	IV

NOTES:

1. For cases with lymph node involvement with no evidence of primary tumor (eg, T0 N1, etc) or with breast ductal carcinoma *in situ* (eg, Tis N1, etc), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the pathological prognostic stage group table.

3. The prognostic value of these prognostic stage groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Genomic profile for pathologic prognostic staging

When OncotypeDx score is less than 11...

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the pathological prognostic stage group is...
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

NOTES:

1. Obtaining genomic profiles is NOT required for assigning pathological prognostic stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned pathological prognostic stage group IA.
2. If OncotypeDx is not performed, or if it is performed and the OncotypeDx score is not available, or is 11 or greater for patients with T1-2 N0 M0 HER2-negative, ER-positive cancer, then the prognostic stage group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx is the only multigene panel included to classify pathologic prognostic stage because prospective level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to prognostic stage groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* T1 includes T1mi.

¶ N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Δ N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1, and T4 N1, respectively.

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Graphic 117141 Version 7.0

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