

**EDUCATIONAL OBJECTIVE:** Readers will thoroughly assess breast lumps, regardless of the patient's age**ROBERT WESOŁOWSKI, MD**
Taussig Cancer Institute, Cleveland Clinic**GEORGE THOMAS BUDD, MD***
Taussig Cancer Institute, Cleveland Clinic

A young woman with a breast mass: What every internist should know

A 40-YEAR-OLD premenopausal woman presents with a palpable lump in her left breast. She first noted it 2 months ago on self-examination, and it has steadily grown in size regardless of the phase of her menstrual cycle.

The patient has never undergone mammography. Her menarche was at age 12. At age 35, she had one child (whom she breast-fed) after a normal first full-term pregnancy. She took oral contraceptives for 10 years before her pregnancy. She has no other medical problems. She has no family history of breast or ovarian cancer.

On examination, her breasts are slightly asymmetric, without skin discoloration, tenderness, swelling, nipple retraction, or discharge. A 1.5- to 2-cm, rubbery, mobile lump can be felt in the left breast at about the 2 o'clock position. No axillary lymph nodes can be palpated. The rest of her examination is normal.

■ BREAST CANCER MUST BE RULED OUT

Benign breast disease is found in approximately 90% of women 20 to 50 years of age who come to a physician with a breast problem.¹

Nevertheless, breast cancer is of major concern. It is the most common type of cancer in women in the United States, responsible for an estimated 194,440 new cases and 40,610 deaths in 2009. It is also the leading cause of cancer-related death in women age 45 to 55 years in this country.^{2,3}

Breast cancer is most common in postmenopausal women, its incidence rising sharply after the age of 45 and leveling off at age 75. The

median age at diagnosis is 61 years. Still, 1.9% of breast cancers in women are diagnosed at age 20 to 34, 10.6% at age 35 to 44, and 22.4% at age 45 to 54.⁴

Thus, it is paramount to perform a thorough assessment and workup of women who have breast lumps, regardless of their age. Doing so allows breast cancer to be detected at an early stage. The 5-year survival rate is 98.0% for women with localized disease, 83.6% with regional disease, and 23.4% with distant disease.⁴

■ WHAT IS THE APPROPRIATE WORKUP?

1 Which of the following are appropriate in the workup of this patient?

- Mammography
- Ultrasonography
- Percutaneous needle biopsy of the lesion
- Magnetic resonance imaging (MRI) of the brain
- Computed tomography (CT) of the chest, abdomen, and pelvis
- Positron emission tomography (PET)

She should undergo mammography, ultrasonography, and percutaneous needle biopsy.

Physical findings that suggest breast cancer include a hard, isolated, sometimes nonmobile lump, serosanguinous nipple discharge, and unilateral nipple retraction. Peau d'orange skin discoloration can occur. A scaly, vesicular, or ulcerated rash with or without pruritus, burning, irritation, or pain of the nipple or skin (Paget disease of the breast) is found in 1% to 3% of breast cancers and may be initially dismissed as mastitis.^{5,6} Palpable enlarged axillary lymph nodes can suggest invasive breast cancer.

Mammography is recommended in all

5-year survival rates in women with breast cancer:
localized, 98.0%;
regional, 83.6%;
distant, 23.4%

*Dr. Budd has disclosed that he serves on advisory boards for Amgen, Pfizer, Roche, and Sanofi-Aventis.

doi:10.3949/ccjm.77a.09095

cases of suspicious breast lumps. In a patient with a palpable lump, diagnostic mammography has a positive predictive value of 21.8%, a specificity of 85.8%, and a sensitivity of 87.7%, which are higher values than in a patient without signs or symptoms.⁷

The BIRADS score. Mammographic findings are summarized using a scoring system devised by the American College of Radiology called BIRADS (Breast Imaging Reporting and Data System). This system is based on mass irregularity, density, spiculation, and presence or absence of microcalcifications. It standardizes the results of mammography, gives an estimate of the risk of breast cancer, and recommends the frequency of follow-up examinations.⁸ Scores range from 0 to 6:

- 0—Incomplete assessment warranting additional evaluation
- 1—Completely negative mammogram
- 2—Benign lesion
- 3—Requires follow-up mammogram at 6 months
- 4—Risk of cancer is 2% to 95%; core biopsy needed
- 5—Risk of cancer is more than 95%; core biopsy needed
- 6—Cases that have already been proven to be malignant.

Ultrasonography is also done if a suspicious lesion is found on mammography or physical examination. It helps differentiate between solid and cystic masses. If a mass is identified as a cyst, ultrasonography can further characterize it as simple, complicated-simple, or complex. Simple cysts and complicated-simple cysts are unlikely to be malignant.^{9,10} Complex cysts or cysts associated with solid tissue are evaluated by biopsy.

Percutaneous needle biopsy should be done for a definitive diagnosis of most suspicious breast masses.

MRI can sometimes provide more accurate information about the possibility of multifocal breast cancer by revealing additional lesions missed on mammography or ultrasonography. It is also useful in determining more accurately the size of the breast tumor and looking for any possible contralateral lesions. In addition, it can sometimes detect enlarged axillary lymph nodes. However, it has poor specificity for breast cancer and may lead to additional

and sometimes unnecessary diagnostic tests, which can delay treatment.

MRI's role is therefore not clearly established, but it is commonly used in clinical practice. It is argued that workup of MRI findings may help in planning more accurate surgical procedures and may prevent reoperations. Based on retrospective analyses, results of breast MRI may lead to altered surgical treatment in approximately 13% of patients.¹¹

Interestingly, a recent randomized trial showed no difference in reoperation rates between patients who underwent MRI before surgery vs those who did not. However, diagnostic workup of new MRI findings was not mandated by the study protocol, making the results of this trial difficult to interpret.¹²

■ DIFFERENTIAL DIAGNOSIS

2 Which of the following is in the differential diagnosis of a woman presenting with a breast abnormality?

- Fibrocystic changes
- Breast cyst
- Ductal ectasia
- Simple fibroadenoma
- Intraductal papilloma
- Ductal carcinoma in situ
- Mastitis
- Infiltrating ductal carcinoma
- Phyllodes tumor

All of these choices are part of the differential diagnosis.

Benign breast lesions

Benign breast lesions are divided into those that are proliferative and those that are nonproliferative. Some (but not all) proliferative lesions pose a higher risk of progressing to malignancy than nonproliferative lesions do.¹³ Benign breast lesions that do not increase the risk of breast cancer are listed in **TABLE 1**.

Simple fibroadenoma, one of the most common proliferative lesions, is not associated with a higher risk of developing breast cancer.

Fibrocystic changes are the most common nonproliferative lesions. Occasionally breast pain, nipple discharge, or significant lumpiness that varies during the course of the menstrual cycle can occur. The nipple discharge in

MRI has poor specificity for breast cancer and may lead to additional testing, delaying treatment

women with fibrocystic changes is physiologic and pale green to brown in color. It can also be yellow, whitish, clear, or bloody. Bloody nipple discharge is considered pathologic and suggests a process other than fibrocystic changes, necessitating further workup. However, bloody discharge is not always a sign of malignancy, as it can have a benign cause as well.

Ductal ectasia, another nonproliferative lesion, is a result of dilation of subareolar ducts that contain fluid with a crystalline material. It can penetrate the duct, forming a nodule, which causes pain and occasionally fever.

Precancerous and cancerous lesions

Lesions that can increase the risk of breast cancer are listed in **TABLE 2**. The degree of risk depends on the complexity and amount of atypia found on the biopsy specimen. The relative risk of developing breast cancer in patients with simple proliferative lesions without atypia is 1.6 to 1.9, compared with 3.7 to 5.3 for complex lesions with high degrees of atypia.¹⁴

Ductal carcinoma in situ is a true neoplasm that has not yet developed the ability to invade through the basement membrane of the ducts. The likelihood of progression to invasive breast cancer depends on the histologic grade, the tumor size, and the patient's age.

Lobular carcinoma in situ arises from lobules and terminal ducts of breast tissue. Much controversy surrounds this type of tumor, which was thought to be a marker of increased risk of developing ipsilateral and contralateral breast cancer and not to be a malignant lesion itself.¹⁵ However, there is emerging evidence to suggest that a pleomorphic variant of lobular carcinoma in situ is associated with development of breast cancer in the same site as the lesion, whereas a nonpleomorphic form is a marker of increased risk of ipsilateral and contralateral breast cancer.¹⁶

Invasive ductal and lobular carcinomas are the true invasive breast cancers, with a potential to metastasize.

Phyllodes tumors are uncommon fibroepithelial lesions that account for less than 1% of all breast neoplasms. The median age at presentation is 45 years.¹⁷ Despite the historical name "cystosarcoma phyllodes," these lesions are not true sarcomas and have stromal and epithelial components.

TABLE 1

Benign breast lesions not associated with a higher risk of breast cancer

Fibrocystic changes

Most common
No discrete lesions on physical examination

Simple fibroadenoma

Common proliferative lesion

Ductal ectasia

Dilated mammary duct that can produce pain, fever, and occasionally a subareolar nodule

Superficial thrombophlebitis of the thoracoepigastric vein (Mondor disease)

Can develop spontaneously or result from trauma
Although not associated with malignancy itself, it may be present in patients with underlying cancer (mammography is recommended in women under age 35)

Breast abscess

Painful, fluctuant to palpation, occasionally with skin discoloration
Most common in breastfeeding women

Pseudoangiomatous stromal hyperplasia

Rare, benign, stromal proliferation
May mimic other vascular lesions such as angiosarcoma

Galactocele

Obstructed mammary duct

Diabetic mastopathy

Occurs in type 1 diabetic patients who also have neuropathy and retinopathy
Mammography reveals a dense lesion

Other, uncommon lesions

Hamartoma
Lipoma
Squamous apocrine metaplasia
Tubular adenoma
Neurofibroma
Sarcoidosis

These tumors display very heterogeneous behavior and, based on predefined histologic criteria, are often classified as benign, borderline, or malignant. Benign phyllodes tumors are similar to fibroadenomas in both histology and prognosis, making their diagnosis challenging. The most aggressive phyllodes tumors lose their epithelial component and have high metastatic potential. These tumors often have a biphasic growth pattern, and women may present with a smooth, round, well-defined

TABLE 2

Breast lesions associated with a higher risk of breast cancer

Ductal hyperplasia

Without atypia: frequently increased number of epithelial ductal cells with benign features
Atypical: uniform ductal cells with loss of apical-basal cellular orientation; precursor of invasive breast cancer

Sclectrosing adenosis

Hyperplastic change of lobules with increased fibrous tissue and interspersed glandular cells

Diffuse papillomatosis

Refers to the occurrence of multiple papillomas

Complex fibroadenomas

Cysts larger than 3 mm, sclerosing adenosis, epithelial calcification, or papillary apocrine changes
Risk of breast cancer rises when proliferative changes are detected in surrounding breast tissue

Radial scars

Fibroelastic core with radiating ducts and lobules
Often found incidentally on surgical pathology
Spiculated mass on mammogram if large enough
Conflicting evidence about association with a higher risk of breast cancer

Atypical lobular hyperplasia

Similar to lobular carcinoma in situ but less developed quantitatively
Historically, an indicator of risk of development of neoplasm
Recent evidence indicates that it may be premalignant

Hormone replacement therapy should be used selectively, to treat symptoms, and only for the short term

breast lump that was stable for many years but then started to grow rapidly.¹⁷

Surgical resection with wide margins is the primary management of these tumors.¹⁸

Mastitis, ie, inflammation of the breast tissue, often presents with symptoms of breast erythema, swelling, tenderness, and nipple discharge. It may be secondary to infection (most often in lactating women) or other causes such as radiation or underlying malignancy. A complication of infectious mastitis is formation of a breast abscess. Underlying malignancy, especially inflammatory breast cancer, is a common cause of noninfectious mastitis and is very important to recognize.¹⁹

RISK FACTORS FOR BREAST CANCER

3 Which of the following are risk factors for breast cancer?

- Menarche before age 12
- Female sex
- Personal history of breast cancer
- Obesity
- Never having had children, or having given birth for the first time at an older age

- Older age
- History of hormone replacement therapy with estrogen and progesterone
- Family history of breast cancer

All of these choices are risk factors for breast cancer.

Family history

The overall relative risk of developing breast cancer in a woman with a first-degree relative with the disease is 1.7. However, the relative risk is about 3 if the first-degree relative developed breast cancer before menopause, and 9 if the first-degree relative developed bilateral breast cancer before menopause.⁵

Familial syndromes are a major factor in 5% to 7% of cases of breast cancer. Most frequently, they involve mutations in the BRCA1 and BRCA2 genes, which encode DNA excision repair proteins. Such mutations are present in about 2.2% of the Ashkenazi Jewish population, and carriers have a lifetime risk of developing breast cancer of 56% to 85%.^{20,21} Other common familial syndromes associated with breast cancer include the Cowden and Li-Fraumeni syndromes (TABLE 3).²²⁻²⁵

Estrogen exposure

The duration and amount of estrogen exposure are also risk factors. For example, menarche before age 12 and menopause after age 55 are associated with a higher risk. Women who go through menopause after age 55 have a twofold higher risk of breast cancer compared with women who go through menopause at an early age. Pregnancy before age 30 lowers the risk of breast cancer; late first full-term pregnancy or nulliparity increases it. Lactation, on the other hand, has a protective effect.⁵

Oral contraceptives have traditionally been thought to increase the risk of breast cancer. In the 1990s, a meta-analysis involving 153,506 women found that those who had used oral contraceptives had a 24% higher risk of developing breast cancer.²⁶ However, this association has come into question since newer oral contraceptive pills containing different progestins and lower amounts of estrogen have become available. In fact, recent studies showed no link between oral contraceptive use and breast cancer.^{27,28} Nevertheless, women at higher risk of developing breast cancer are advised not to use oral contraceptives.

Hormone replacement therapy with estrogen and progesterone was found to increase the risk of breast cancer by 26% in the Women's Health Initiative (WHI) study, which involved 16,608 healthy women followed for a median of 5.6 years.²⁹

In a study reported separately, the WHI investigators randomized 10,739 women who had undergone hysterectomy to receive either hormone replacement therapy with unopposed estrogen (which is feasible only in women without a uterus) or placebo. They found no increase in the risk of invasive breast cancer in women on hormone replacement therapy with estrogen alone. In fact, the study showed a trend towards a modest reduction of this risk (odds ratio 0.77; 95% confidence interval 0.59–1.01).³⁰

After the results of the WHI were published, the use of hormone replacement therapy in postmenopausal women declined significantly. And in 2003—1 year later—the incidence of breast cancer had dropped by 6.7%.³¹

TABLE 3

Familial syndromes associated with breast cancer

Mutations in BRCA1 (chromosome 17) and BRCA 2 (chromosome 13) genes

Lifetime risk of developing breast cancer is 56% to 85%

Lifetime risk of ovarian cancer is 39% to 46% with BRCA1, and 19% with BRCA2

Also increase risk of pancreatic cancer, prostate cancer, and melanoma

Cowden syndrome

(Due to mutation in PTEN tumor suppressor gene on chromosome 10)

Skin lesions (trichilemmomas)

Mucocutaneous hamartomas

Acral skin keratoses

Benign breast lesions

Gastrointestinal polyps

Nonmedullary thyroid cancer (about 10%)

Breast cancer (25% to 50% of carriers)

Endometrial cancer

Renal cancer

Li-Fraumeni syndrome

(An autosomal dominant disorder that is often the result of a p53 mutation on chromosome 17p)

Some cases are due to mutations in the CHEK2 gene (G2 checkpoint kinase)

Premenopausal breast cancer (about 22% of carriers)

Childhood sarcoma

Brain tumors

Leukemia

Adrenocortical carcinoma

Ataxia telangiectasia

(Due to mutation of ATM tumor-suppressor gene on chromosome 11)

Neurologic abnormalities (ataxia)

Oculocutaneous telangiectasias

Immune deficiency

Insulin resistance

Malignancies (mainly lymphoproliferative)

Possibly, a twofold increased risk of breast cancer

Peutz-Jeghers syndrome

(Mainly due to mutation in STK11, a threonine kinase gene on chromosome 11)

Hamartomatous polyps in the gastrointestinal tract

Mucocutaneous melanin deposits in buccal mucosa, lips, and extremities

Increased risk of gastrointestinal malignancy

Higher rates of extraintestinal cancers

Hereditary diffuse gastric cancer

(Mutations in E-cadherin gene in about 48% of cases)

Diffuse-type gastric cancer

Colon cancer

Infiltrating lobular carcinoma (20%–54% of patients with E-cadherin mutation)

Most experts now recommend that estrogen-progestin combinations be used only selectively to treat the symptoms of menopause, and only for the short term.

Other risk factors

Other factors found to modestly increase the risk of breast cancer include:

- Alcohol use
- Obesity
- Radiation exposure. Patients are at higher risk of breast cancer 15 to 20 years after receiving upper-mantle radiotherapy for Hodgkin lymphoma.⁵

Case continues: Bad news on mammography, ultrasonography, biopsy

The patient undergoes mammography, which shows a 2.5-cm spiculated lesion with areas of calcifications (BIRADS score of 5). Subsequently, ultrasonography confirms that the suspicious mass is not a cyst. Ultrasound-guided core needle biopsy reveals that the lesion is a high-grade invasive ductal carcinoma. The tumor is positive for both estrogen and progesterone receptors and negative for HER2/neu overexpression.

■ STAGING EVALUATION

4 Given these findings, what is the next step to take?

- CT of the chest, abdomen, and pelvis
- MRI of the brain
- PET
- Referral to a surgeon for a possible mastectomy with sentinel lymph node dissection
- Referral to a surgeon for a possible lumpectomy with sentinel lymph node dissection

At this point, the patient should be referred to a surgeon for possible mastectomy or lumpectomy.

Women who appear clinically to have early breast cancer, such as in this case, should have a complete blood count, comprehensive metabolic panel, and chest x-ray as their initial staging evaluation. No further studies are recommended unless the findings on history, physical examination, or the above testing suggest possible metastases.

Mastectomy vs lumpectomy

Early-stage breast cancer is managed with definitive surgery. The two options are mastectomy and breast conservation therapy, the latter involving lumpectomy followed by breast radiation therapy.

Multiple randomized studies comparing mastectomy and lumpectomy showed no difference in survival rates, but patients in the lumpectomy groups had higher rates of local recurrence.³² Breast radiation therapy after lumpectomy lowered the rates of local recurrence and breast cancer death.³³ Therefore, most patients can opt to undergo either lumpectomy with radiation or mastectomy, depending on personal preference.

However, mastectomy rather than breast conservation therapy is still recommended in cases of prior radiation therapy, inability to achieve negative surgical margins (as in cases of large tumors), multicentric disease (cancer in separate breast quadrants), or multiple areas of calcifications. Mastectomy is also preferred in most pregnant women unless the diagnosis of breast cancer is made in the third trimester and radiation therapy can be given after delivery. Patients who have large lesions in a small breast may also choose mastectomy with breast reconstruction rather than breast conservation therapy. Patients with a history of scleroderma are encouraged to undergo mastectomy because of increased toxicity from radiation treatment.

Sentinel vs axillary lymph node dissection

Knowledge of axillary lymph node involvement is important because it determines the stage in the tumor-node-metastasis (TNM) system, and it influences the choice of further therapy. Therefore, all patients with nonmetastatic invasive breast cancer must have their axillary lymph nodes sampled.

Conventionally, this involves axillary lymph node dissection. Unfortunately, upper extremity lymphedema develops in 6% to 30% of patients within the first 3 years, and in 49% of patients after 20 years following axillary lymph node dissection.³⁴

Sentinel lymph node dissection was developed to minimize this complication. This procedure involves the injection of a blue dye, isosulfan blue (Lymphazurin), around the edge

Most patients can opt for either lumpectomy with radiation or mastectomy, depending on their personal preference

of the tumor or in the dermis overlying the tumor. The most proximal axillary lymph nodes that stain blue are dissected. Alternatively, a radioactive colloid (most commonly technetium sulfur colloid agents) may be injected, allowing sentinel lymph nodes to be identified by lymphoscintigraphy. If no metastases are found in the sentinel lymph nodes, axillary lymph node dissection is not performed.

A prospective study in 536 women found that at 5 years of follow-up, lymphedema developed in only 5% of patients after sentinel lymph node dissection compared with 16% of those who underwent axillary lymph node dissection ($P < .001$), with comparable outcomes in terms of disease recurrence.³⁵

Case continues: Patient undergoes surgery

The patient elects to undergo lumpectomy with sentinel lymph node dissection. Pathologic review of the resection specimen reveals a 2.5-cm poorly differentiated invasive ductal carcinoma. Sentinel lymph node dissection shows metastases, and therefore axillary lymph node dissection is performed. One of eight lymph nodes removed is positive for metastases. All surgical margins are negative.

■ POSTOPERATIVE CARE

5 What would be the next step for our patient?

- Radiation followed by observation
- Tamoxifen (Nolvadex) for 5 years
- Observation only
- Chemotherapy followed by radiation therapy and 5 years of tamoxifen

She should receive chemotherapy, followed by radiation therapy and then tamoxifen for 5 years.

Chemotherapy. Almost all patients who have lymph-node-positive disease are advised to undergo chemotherapy.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-analysis of 194 randomized trials that compared adjuvant chemotherapy and no treatment in early-stage breast cancer. Chemotherapy led to a 10% absolute improvement in survival at 15 years for women younger than 50 years and 3% in women age 51 to 69.³⁶

Indications for chemotherapy include axillary lymph node involvement, locally advanced disease, and other risk factors for recurrence such as young age at diagnosis, strong positive family history of breast cancer, prior history of breast cancer, or lymph-node-negative, estrogen-receptor-negative tumors that are larger than 1 cm in diameter.

The Oncotype DX assay is a new tool to help oncologists decide whether to use chemotherapy in cases of estrogen-receptor-positive breast cancer, in which the benefit of chemotherapy is uncertain. It is a polymerase chain reaction assay that measures the expression of 16 cancer-specific genes and five reference genes within the breast tumor. Based on the pattern of expression of these genes, breast cancer can be characterized as low-risk, intermediate-risk, or high-risk. Patients in the high-risk group have a high chance of cancer recurrence and benefit from chemotherapy. Patients in the low-risk group are unlikely to have a recurrence or to benefit from chemotherapy.³⁷ It is far less clear if patients in the intermediate-risk group benefit from chemotherapy, but this assay might eventually prove useful in deciding for or against chemotherapy in this group of patients as well.³⁸ The Oncotype DX assay is presently being studied in a clinical trial.

Radiation therapy after mastectomy is recommended in patients who have breast tumors larger than 5 cm or metastases to more than three axillary lymph nodes.³⁹

Antiestrogen therapy. After chemotherapy, patients with estrogen-receptor-positive cancers also receive 5 years of antiestrogen therapy. Available antiestrogen agents for such patients include tamoxifen, which is a selective estrogen receptor modulator, and drugs called aromatase inhibitors that block conversion of androgens to estrogens in peripheral tissues. Anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are examples of available aromatase inhibitors. Premenopausal women are treated with tamoxifen, and postmenopausal women are offered aromatase inhibitors.

The EBCTCG meta-analysis found a 12% absolute reduction in mortality rates and a 9% absolute reduction in relapse rates at 15 years of follow-up in patients who took tamoxifen for 5 years.³⁶

Fewer women develop lymphedema after sentinel node dissection than after axillary node dissection

TABLE 4

Most common adverse effects of hormonal therapy for breast cancer

AGENT	MODE OF ACTION	IMPORTANT ADVERSE EVENTS
Tamoxifen (Nolvadex)	Selective estrogen receptor modulator Antiestrogen in breast, proestrogen in bone, uterus, and platelets	Hot flashes (3%–80%) Flushing (33%–41%) Vaginal discharge (13%–55%) Fluid retention (32%) Arthralgia (11%) Cataracts (7%) Venous thromboembolism (5%) Myocardial infarction (1%) Risk of endometrial cancer (< 1%) No increase in risk of osteoporosis
Anastrozole (Arimidex)	Nonaromatic aromatase inhibitor	Vasodilatation (25%–36%) Hot flashes (12%–36%) Nausea (11%–19%) Arthralgia (17%) Osteoporosis (11%) Cataracts (6%) Myalgia (2%–6%) Vaginal dryness (about 4%) Venous thromboembolism (3%–4%)
Letrozole (Femara)	Nonaromatic aromatase inhibitor	Hot flashes (5%–50%) Night sweats (14%) Arthralgia (8%–22%) Nausea (9%–17%) Myalgia (6%–7%) Osteoporosis (2%–7%) Vaginal dryness/hemorrhage (about 5%) Venous thromboembolism (< 2%)
Exemestane (Aromasin)	Aromatic aromatase inhibitor	Arthralgias (15%–29%) Hot flashes (13%–21%) Vomiting (7%) Osteoporosis (about 5%) Venous thromboembolism (< 1%)

INFORMATION OBTAINED FROM PACKAGE INSERTS.

Premenopausal women are treated with tamoxifen; postmenopausal women are offered aromatase inhibitors

TABLE 4 lists the most common adverse effects of these agents. Aromatase inhibitors are associated with a higher risk of osteoporosis and arthralgia, while tamoxifen increases the risks of thromboembolism, endometrial cancer, and vaginal discharge. Both agents may produce menopausal symptoms such as hot flashes and mood swings.

Case continues:

Seven years later, metastases in the spine

The patient achieves a complete remission. She is seen for a routine visit 7 years after diagnosis. She now reports mid-back pain that has worsened over the last 2 months. A bone scan reveals diffuse metastatic disease in the spine and in both humeral bones. CT of the

chest, abdomen, and pelvis is negative for visceral metastases. Bone marrow aspiration and biopsy study show marrow infiltration by adenocarcinoma that stains positive for estrogen receptors and negative for HER2. The patient otherwise feels well and has no other symptoms.

■ WHAT TREATMENT FOR METASTATIC BREAST CANCER?

6 What should you now do for our patient?

- Discuss end-of-life care and refer her to a hospice program
- Educate the patient that no options for treatment exist and recommend enrolling in a phase I clinical trial
- Refer her to an oncologist for consideration of chemotherapy
- Refer her to an oncologist for consideration of endocrine treatment

She should be referred to an oncologist for consideration of endocrine treatment.

The most common sites of breast cancer metastases are the bones, followed by the liver and lungs. Metastatic breast cancer almost always is incurable. However, treatment can palliate symptoms.

Although a randomized trial of treatment vs best supportive care has never been done, many believe that treatment may improve survival.⁴⁰ The median survival of patients treated with standard therapy is about 3 years if the breast cancer is estrogen-receptor-positive and 2 years if it is estrogen-receptor-negative, but survival rates vary widely from patient to patient.^{41,42}

Standard therapy or enrollment in a clinical phase II or III trial is indicated for this patient before considering enrollment in a phase

I clinical trial or supportive care alone.

Endocrine therapy is the first-line therapy in women with estrogen-receptor-positive metastatic breast cancer. Postmenopausal women usually receive an aromatase inhibitor first.^{43,44} Response to endocrine therapy usually takes weeks to months but may last for several years.

Pre-menopausal women with estrogen-receptor-positive breast cancer also receive ovarian ablation therapy (oophorectomy or chemical ovarian ablation) with gonadotropin-releasing hormone agonists.

In addition, most patients with bone involvement are treated with high doses of intravenous bisphosphonates, which can reduce skeletal complications.⁴⁵

Chemotherapy is reserved for patients with estrogen-receptor-negative breast cancer and those with cancer that progresses despite treatment with multiple antiestrogen agents. The time to response when chemotherapy is used is quicker, but the duration of response is usually shorter, lasting on average less than 1 year.³⁷

Trastuzumab (Herceptin), a monoclonal humanized murine antibody to the extracellular domain of the HER2 protein, is indicated in patients with HER2-overexpressing tumors.^{46,47}

■ STABLE 2 YEARS LATER

The patient was started on letrozole and a bisphosphonate, zoledronic acid (Zometa). Ovarian ablation was initiated with goserelin (Zoladex) given monthly. A bone scan performed 2 months after starting treatment showed improvement in bony metastases. She also noted significant improvement in pain. Her disease remains stable 2 years after starting endocrine therapy. ■

Metastatic breast cancer is almost always incurable, but treatment can palliate symptoms

■ REFERENCES

1. Barton MB, Elmore JG, Fletcher SW. Breast symptoms among women enrolled in a health maintenance organization: frequency, evaluation, and outcome. *Ann Intern Med* 1999; 130:651–657.
2. Petrelli NJ, Winer EP, Brahmer J, et al. Clinical cancer advances 2009: major research advances in cancer treatment, prevention, and screening—a report from the American Society of Clinical Oncology. *J Clin Oncol* 2009; 27:6052–6069.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics 2008. *CA Cancer J Clin* 2008; 58:71–96.
4. National Cancer Institute. SEER Stat Fact Sheets. www.seer.cancer.gov/statfacts/html/breast.html#ref09. Accessed June 7, 2010.
5. Puzdur R, Wagman LD, Camphausen KA, Hoskins WJ; the publishers of the journal *Oncology*. *Cancer Management: A multidisciplinary Approach*. Medical, Surgical & Radiation Oncology. 11th ed. CMP Medica; 2008.
6. Kollmorgen DR, Varanasi JS, Edge SB, Carson WE 3rd. Paget's disease of the breast: a 33-year experience. *J Am Coll Surg* 1998; 187:171–177.
7. Barlow WE, Lehman CD, Zheng Y, et al. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. *J Natl Cancer Inst* 2002; 94:1151–1159.

8. **American College of Radiology.** Breast Imaging Reporting and Data System: BIRADS Atlas. 4th ed. Reston, VA: American College of Radiology; 2003.
9. **Hong AS, Rosen EL, Soo MS, Baker JA.** BI-RADS for sonography: positive and negative predictive values of sonographic features. *AJR Am J Roentgenol* 2005; 184:1260–1265.
10. **Berg WA, Campassi CI, Ioffe OB.** Cystic lesions of the breast: sonographic-pathologic correlation. *Radiology* 2003; 227:183–191.
11. **Schell AM, Rosenkranz K, Lewis PJ.** Role of breast MRI in the preoperative evaluation of patients with newly diagnosed breast cancer. *AJR Am J Roentgenol* 2009; 192:1438–1444.
12. **Turnbull L, Brown S, Harvey I, et al.** Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010; 375:563–571.
13. **Worsham MJ, Abrams J, Raju U, et al.** Breast cancer incidence in a cohort of women with benign breast disease from a multiethnic, primary health care population. *Breast J* 2007; 13:115–121.
14. **Dupont WD, Page DL.** Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; 312:146–151.
15. **Page DL, Kidd TE Jr, Dupont WD, Simpson JF, Rogers LW.** Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. *Hum Pathol* 1991; 22:1232–1239.
16. **Sneige N, Wang J, Baker BA, Krishnamurthy S, Middleton LP.** Clinical, histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. *Mod Pathol* 2002; 15:1044–1050.
17. **Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW.** Phyllodes tumors of the breast: natural history, diagnosis, and treatment. *J Natl Compr Canc Netw* 2007; 5:324–330.
18. **Reinuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K.** The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. *Cancer* 1996; 77:910–916.
19. **Kamal RM, Hamed ST, Salem DS.** Classification of inflammatory breast disorders and step by step diagnosis. *Breast J* 2009; 15:367–380.
20. **Hartge P, Struwing JP, Wacholder S, Brody LC, Tucker MA.** The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet* 1999; 64:963–970.
21. **Wooster R, Weber BL.** Breast and ovarian cancer. *N Engl J Med* 2003; 348:2339–2347.
22. **Clarke-Pearson DL.** Clinical practice. Screening for ovarian cancer. *N Engl J Med* 2009; 361:170–177.
23. **Hisada M, Garber JE, Fung CY, Fraumeni JF Jr, Li FP.** Multiple primary cancers in families with Li-Fraumeni syndrome. *J Natl Cancer Inst* 1998; 90:606–611.
24. **Bell DW, Varley JM, Szydio TE, et al.** Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. *Science* 1999; 286:2528–2531.
25. **Kaurah P, MacMillan A, Boyd N, et al.** Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA* 2007; 297:2360–2372.
26. **Collaborative Group on Hormonal Factors in Breast Cancer.** Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; 347: 1713–1727.
27. **Hankinson SE, Colditz GA, Manson JE, et al.** A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States). *Cancer Causes Control* 1997; 8:65–72.
28. **Marchbanks PA, McDonald JA, Wilson HG, et al.** Oral contraceptives and the risk of breast cancer. *N Engl J Med* 2002; 346:2025–2032.
29. **Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321–333.
30. **Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee.** Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291:1701–1712.
31. **Ravdin PM, Cronin KA, Howlader N, et al.** The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007; 356:1670–1674.
32. **Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM.** Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995; 333:1456–1461.
33. **Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 366:2087–2106.
34. **Petrek JA, Senie RT, Peters M, Rosen PP.** Lymphedema in a cohort of breast carcinoma survivors 20 years after diagnosis. *Cancer* 2001; 92:1368–1377.
35. **McLaughlin SA, Wright MJ, Morris KT, et al.** Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol* 2008; 26:5213–5219.
36. **Early Breast Cancer Trialists' Collaborative Group (EBCTCG).** Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365:1687–1717.
37. **Paik S, Shak S, Tang G, et al.** A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; 351:2817–2826.
38. **Albain KS, Barlow WE, Shak S, et al; Breast Cancer Intergroup of North America.** Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010; 11:55–65.
39. **Harris JR, Halpin-Murphy P, McNeese M, Mendenhall NP, Morrow M, Robert NJ.** Consensus Statement on postmastectomy radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; 44:989–990.
40. **Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P.** Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 2005; 104:1742–1750.
41. **Mouridsen H, Gershonovich M, Sun Y, et al.** Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21:2101–2109.
42. **Gamucci T, D'Ottavio AM, Magnolfi E, et al.** Weekly epirubicin plus docetaxel as first-line treatment in metastatic breast cancer. *Br J Cancer* 2007; 97:1040–1045.
43. **Bonnetere J, Thürlimann B, Robertson JF, et al.** Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; 18:3748–3757.
44. **Nabholtz JM, Buzdar A, Pollak M, et al.** Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *Arimidex Study Group.* *J Clin Oncol* 2000; 18:3758–3767.
45. **Hortobagyi GN, Theriault RL, Porter L, et al.** Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *Protocol 19 Aredia Breast Cancer Study Group.* *N Engl J Med* 1996; 335:1785–1791.
46. **Romond EH, Perez EA, Bryant J, et al.** Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353:1673–1684.
47. **Slamon DJ, Leyland-Jones B, Shak S, et al.** Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344:783–792.

ADDRESS: George Thomas Budd, MD, Taussig Cancer Center, R35, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail buddg@ccf.org.