38 BREAST CANCER

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Traditionally, medical students and residents have described difficulty in mastering the topic of breast cancer. This is likely the result of an unwarranted emphasis on various aspects of breast cancer therapy. An acquired knowledge in pretreatment aspects of breast cancer—epidemiology, pathophysiology, surveillance, and diagnosis—would actually find greater utility. With the majority of medical students and residents completing their training and practicing in nononcologic fields, their greatest contribution will be in encouraging screening and subsequent early detection and in providing early referral to a definitive medical specialist (radiation, medical, or surgical oncologist). As medical resources become increasingly scarce, surveillance for recurrence of breast cancer patients may be added to these responsibilities. Thus, this chapter is directed toward the elucidation of (1) the natural history of breast cancer, (2) breast cancer surveillance, (3) risk factors for the development of breast cancer and their effect on surveillance guidelines, (4) abnormal breast cancer surveillance criteria, (5) diagnostic management of abnormal breast cancer surveillance results, and (6) breast cancer risk factors and recurrence sites.

CASE 1
BREAST MASS

A 49-year-old white female with new onset of a right breast mass was referred for evaluation. Further questioning identified a 2-month history without change in size of the mass. A history of local trauma, prior breast biopsy (demonstrating atypical lobular/ductal hyperplasia), mother or sister with breast cancer, and previous screening mammogram were denied. Physical examination revealed a mobile 2 × 2-cm dominant upper outer quadrant right breast mass without associated skin changes. FNA cytology was performed and initial screening mammography requested. Having had the requested screening mammogram, the patient returned for her follow-up appointment 1 week later. The FNA showed infiltrating ductal carcinoma. The mammogram demonstrated a right upper outer quadrant stellate density, suspicious for malignancy, that correlated with the position of the physical finding.

The patient was advised of the diagnosis of breast cancer along with treatment options for early breast cancer. Metastatic workup was requested, which was negative. The patient elected breast preservation and underwent surgical lumpectomy with axillary lymphadenectomy. Final pathology confirmed infiltrating ductal carcinoma with negative margins on the lumpectomy and 1 of 21 axillary lymph nodes involved with cancer (T1, NI, M0, stage IIA). Following hospital discharge and wound healing, medical and radiation oncology consultations were

arranged. Adjuvant chemotherapy and breast irradiation were planned and completed within 6 months. Recurrence surveillance was outlined and initiated.

CASE 2
OCCULT LESION

A 64-year-old black female had a new mammographic lesion identified on her most recent annual screening mammogram. Her primary care physician referred her for surgical oncology consultation. She had undergone annual screening mammography since age 50. All prior mammograms were reported to be normal. A history of local trauma, prior breast biopsy (demonstrating atypical lobular/ductal hyperplasia), and mother or sister with breast cancer were denied. Physical examination revealed no dominant mass, nipple discharge, or skin changes. Review of the recent mammogram, with comparison to prior mammograms, was performed by both surgical oncologist and dedicated mammographer. The mammographic lesion was confirmed as new, highly suspicious for malignancy (new density with irregular borders), and warranting a tissue diagnosis through needle localization biopsy.

The patient was advised of the findings and recommendations. Needle localization biopsy revealed benign fibrocystic changes without evidence of neoplasm. One week later she was seen in order to evaluate wound healing, advise her of the final diagnosis, and schedule a 1-month wound check and new baseline unilateral mammogram (to be performed between 1 and 3 months postbiopsy). The next screening breast physical and mammographic examinations were scheduled for 1 year.

GENERAL CONSIDERATIONS

Breast cancer is the number one malignancy in women. It ranks second to lung cancer in cancer-related deaths. Currently, one out of every eight women will be diagnosed with breast cancer within her lifetime. The incidence continues to rise at a rapid pace, and it is estimated that 183,400 new cases of breast cancer will be diagnosed in 1995 (182,000 in women and 1,400 in men) in the United States.

A well-defined etiology is present in less than 10% of all patients diagnosed with breast cancer. A genetic etiology (hereditary breast cancer) may be demonstrated by a family history of breast cancer in one or more first-degree relatives (mother or sister). A positive family history increases the risk of breast cancer fivefold relative to the baseline female population. A similar increase in risk is associated with a history of a prior breast biopsy demonstrating atypical ductal/lobular hyperplasia. (The proliferative cellular pattern found in atypical ductal/lobular hyperplasia may indicate a common proliferative etiology for the development of breast cancer.) However, reported associations between breast cancer development and cigarette smoking, fat intake, alcohol consumption, early menarche, late menopause, and delayed first pregnancy (after age 30) fail to define an etiology or significant association with the development of breast cancer (sporadic breast cancer) in an individual patient, although epidemiologic data suggest their influence.

The relevance of grading risk of breast cancer development is to guide breast cancer surveillance (Table 38.1 and Fig. 37.1). Documentation of a positive family history and/or prior pathologically proven atypical ductal/lobular hyperplasia may require modification of the standard breast cancer surveillance program, although the time interval will not be less than 1 year. Therefore, patients over age 50 require no modification; between age 40 to 50, screening mammography is modified to annual testing; and under age 40, screening mammography is initiated earlier (at intervals of 1–2 years) and breast physical examination performed yearly.

Breast cancer most commonly arises from either ductal or lobular epithelium. Breast sarcomas and lymphomas arise from mesenchymal cells in the supporting structure of the breast. The most common histologic type of breast cancer is infiltrating (invasive) ductal carcinoma. There exist numerous other histologic types; the only value of their recognition is to identify an altered prognosis (e.g., improved prognosis associated with medullary and colloid carcinoma). Noninvasive ductal/lobular carcinoma in situ (DCIS/LCIS) represent cancers that have not invaded the basement membrane.

Carcinoma of the breast spreads by lymphatic and vascular channel permeation and embolization. Common regional lymphatic sites of spread include the axillary, supraclavicular, and internal mammary nodes. The axillary nodal basin is most commonly involved. Although defined as regional lymphatic metastasis, patients without spread beyond this level are referred to as early breast cancer and may be cured of their disease through proper treatment.

TABLE 38.1 *American Cancer Society breast cancer surveillance recommendations*

Test or Procedure	Age (yr)	Frequency
BSE	≥20	Every month
BPE	20–40	Every 3 years
BPE	≥40	Every year
Screening mammography	40	Baseline
	40–49	Every 2 years
	≥50	Every year

Abbreviations: BSE, breast self-examination; BPE, breast physical examination.

The exception is supraclavicular nodal involvement, which is tantamount to distant metastasis. This is supported by the recent inclusion of supraclavicular nodal involvement in M1 disease, as specified by the Tumor, Node, and Metastasis (TNM) staging classification (Table 38.2). Less information regarding internal mammary nodal involvement and prognosis is available. Nevertheless, it would be reasonable to conclude that the addition of internal mammary nodal involvement would bear a worse prognosis, yet still be amenable to cure in the absence of distant metastatic disease.

DCIS/LCIS, by definition, represents noninvasive cancer of the breast ductules and lobules. In the absence of invasion, there exists the risk of local recurrence but not metastasis, with its associated risk to survival. Nevertheless, poorly or untreated DCIS/LCIS may lead to invasive disease, with all the attendant risks of metastatic disease and loss of life.

TABLE 38.2 *Breast cancer staging*

Stage I	T1 N0 M0		T2 N2 M0
Stage IIA	T1 N1 M0		T3 N1 M0
	T2 N0 M0		T3 N2 M0
Stage IIB	T2 N1 M0	Stage IIIB	T4 Any N M0
	T3 N0 M0		Any T N3 M0
Stage IIIA	T0 N2 M0	Stage IV	Any T Any N M1
	T1 N2 M0		

T	Primary tumors
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraductalcarcinoma, lobular carcinoma, or Paget's disease with no tumor
T1	Tumor >2 cm or less in its greatest dimension
T2	Tumor >2 cm but not more than 5 cm in its greatest dimension
T3	Tumor >5 cm in its greatest dimension
T4	Tumor of any size with direct extension to the chest wall or to skin[a]
N	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis to movable ipsilateral axillary node(s)
N2	Metastasis to ipsilateral axillary nodes, fixed to one another or to other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)
M	Distant metastasis
M0	No evidence of distant metastasis
M1	Distant metastases (including metastases to ipsilateral supraclavicular lymph nodes)

[a]Chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not pectoral muscle.

Mammary sarcomas may be classified by histology (liposarcoma, leiomyosarcoma, fibrosarcoma, angiosarcoma, malignant fibrous histiocytoma, and malignant cystosarcoma phyllodes). However, their incidence is rare and biologic behavior so similar that they may be grouped as a whole for consideration of diagnostic and therapeutic intervention. Lymphatic spread is exceedingly rare, obviating the need for diagnostic axillary node dissection. Metastasis occurs by vascular spread with the lungs being the most common distant site of spread.

Primary breast lymphoma is extremely rare. It tends to be larger than mammary carcinoma at the time of diagnosis. There is a high incidence of axillary nodal involvement, which may make it difficult to ascertain whether the tumor is primary or secondary within the breast.

KEY POINTS

- Breast cancer number one malignancy in women, second to lung cancer in cancer-related deaths
- One of every eight women will be diagnosed with breast cancer within her lifetime
- Risk increases with a history of prior breast biopsy demonstrating atypical ductal/lobular hyperplasia
- Grading breast cancer development guides surveillance
- Most common histologic type of breast cancer is infiltrating (invasive) ductal carcinoma
- In DCIS/LCIS, noninvasive cancer of breast ductules and lobules, there exists risk of local recurrence but not metastasis

I DIAGNOSIS

In general, patients with breast cancer present in one of three manners. These include a new (within 2 years) dominant (discrete borders relative to surrounding parenchyma) breast mass identified by the patient (Case 1); a dominant breast mass identified by a physician at breast physical examination; and a dominant density and/or clustered microcalcifications identified at screening mammography (Case 2). Smooth-walled lesions may be examined by ultrasound to differentiate solid from cystic, with solid lesions suspicious for cancer. Densities with irregular borders are suspicious for malignancy and do not warrant ultrasound. Clustered microcalcifications are those greater than five in number. Suspicious microcalcifications are linear and branch-like, not punctate. A less common presentation is that of symptomatic metastatic breast cancer (most common sites for metastatic spread are lung, liver, and bone).

Breast cancer surveillance guidelines have been developed as a result of our knowledge of presentation. As recommended by the American Cancer Society, they include first screening mammogram at age 40; screening mammogram every 2 years through age 50 and yearly thereafter;

breast physical examination by a physician every 3 years between ages 20 to 40 and yearly thereafter; and monthly breast self-examination (Table 38.1) initiated at age 20.

Abnormal surveillance studies warrant a tissue diagnosis (see Fig. 37.1). The preferred method for obtaining a tissue diagnosis is a cytologic diagnosis furnished through fine needle aspiration (FNA). For palpable masses this may be performed on the initial surgical consultation (Case 1). For occult lesions (nonpalpable, identified by mammography only), FNA is only available to select centers that possess a stereotactic mammographic unit. The accuracy of breast FNA is cytopathologist dependent. In the hands of skilled cytopathologists, accurate diagnosis can be rendered for malignant breast neoplasms (cancer more so than sarcoma/lymphoma) and benign neoplasms (fibroadenoma). Less common and somewhat controversial, a benign nonneoplastic (fibrocystic changes) diagnosis can be rendered through FNA alone.

When reliable FNA is unavailable, or insufficient to establish a diagnosis, actual tissue must be retrieved. This can be achieved through either excisional (removal of entire palpable mass or occult lesion) or incisional biopsy (partial removal of a palpable mass when removal would cosmetically alter the breast). A form of incisional biopsy is the core needle biopsy. This can be performed under local anesthesia in the office/clinic at the same time that FNA results (nondiagnostic) are rendered. In centers performing stereotactic breast FNA, concomitant core needle biopsy may be performed.

KEY POINTS

- Patients with breast cancer present with a new, dominant breast mass identified by the patient; a dominant breast mass identified at examination; or a dominant density and/or clustered microcalcifications identified at mammography
- Breast cancer surveillance guidelines recommended by the American Cancer Society, include first mammogram at age 40; mammogram every 2 years through age 50 and annual breast examination by a physician every 3 years between ages 20 to 40 and yearly thereafter; and monthly self-examination, initiated at age 20

B DIFFERENTIAL DIAGNOSIS

Breast cancer surveillance studies are evaluated with an intentionally low threshold to increase their sensitivity. The greater the sensitivity, the greater the biopsy/cancer ratio. A good example of this process is seen in the comparison of biopsy/cancer ratios in Europe and the United States. The biopsy/cancer ratio in the United States is double that seen in Europe. This difference is likely accounted for by this country's current malpractice climate. The European practice of observing low probability mammographic lesions is considered to be prohibitive in the United States.

Breast trauma (with resultant fat necrosis), locally thrombosed veins, benign neoplasms (most commonly fibroadenomas), fibrocystic changes (Case 2), and non-neoplastic inflammation/infection all may mimic breast cancer and present as an abnormal surveillance study. Fortunately, most methods for achieving a tissue diagnosis are minimally invasive without significant risk of disability and/or impaired cosmesis, and allowing for tissue diagnosis and avoidance of potentially delayed diagnosis (associated with a higher threshold).

KEY POINTS

- Breast cancer surveillance studies are evaluated with an intentionally low threshold to increase sensitivity
- The greater the sensitivity, the greater the biopsy/cancer ratio

H TREATMENT

Having established the diagnosis of breast cancer, the extent of disease (stage) must be determined (Case 1). Accurate staging of a patient's breast cancer is necessary for treatment selection and prognosis, as well as outcome comparisons. The TNM classification is the universally accepted staging system currently in use (Table 38.2). TNM permutations are divided into four staging groups (I–IV). Further diagnostic intervention (metastatic workup) is required to complete this process. Diagnostic study selection is based upon the knowledge of common metastatic organ sites (lung-chest x-ray, liver-liver function tests, bone-serum alkaline phosphatase).

Not all stages of breast cancer are curable. Metastatic breast cancer (stage IV) is incurable. All other stages are treatable for cure, yet all are at risk of recurrence/progression with advancement to metastatic disease and ultimate loss of life. Therapeutic intervention is subdivided into local, regional, and systemic therapy. Multimodality therapy (combination of surgery, radiotherapy, chemotherapy, and/or hormonal therapy) is customary. Nevertheless, surgical removal of the local tumor remains common to all therapeutic options performed for cure.

Surgery is a local/regional therapy applied to the primary tumor within the breast and axillary lymph nodes, respectively. Lumpectomy (removal of the breast tumor while preserving the natural cosmetic appearance of the breast) and mastectomy are the two local surgical therapeutic options. Patients with breast cancer are candidates for lumpectomy (breast preservation) as long as the tumor mass can be grossly removed without an unacceptable cosmetic effect. When lumpectomy is followed by breast irradiation, local control and survival are equivalent to mastectomy. With rare

exception, both surgical procedures are associated with an axillary lymph node dissection to identify nodal involvement for TNM classification. (Axillary lymph node dissection is a diagnostic, not therapeutic intervention.)

Radiotherapy is routinely used in association with lumpectomy (Case 1). Adjuvant, postoperative chest wall (in patients who have undergone mastectomy) and supraclavicular fossa irradiation are advised by some when risk of local and regional recurrence is increased (tumor greater than 5 cm in diameter, positive deep margin of breast tumor removal through mastectomy, and/or greater than four axillary lymph nodes involved with tumor). The intention is to reduce the problematic chest wall/regional recurrence, which may be painful, difficult to control when present, and may compromise upper extremity function.

Chemotherapy and hormonal therapy affect systemic disease. Following local/regional treatment of early breast cancer (removal of all gross disease), the patient remains at risk of recurrent local/regional as well as systemic disease. Systemic recurrence occurs secondary to progressive growth at metastatic sites that were present at the initial patient presentation, yet not identifiable through routine metastatic workup. Systemic treatment at this stage is referred to as adjuvant systemic treatment. The earliest role for adjuvant systemic treatment was in treating patients with axillary nodal involvement. Adjuvant systemic treatment of node-positive breast cancer resulted in improved survival. More recently, adjuvant systemic treatment of node-negative breast cancer has similarly demonstrated improved survival. Thus, it is common practice to advise systemic treatment in patients with node-negative as well as node-positive breast cancer (Table 38.3).

Although metastatic breast cancer is incurable, therapeutic intervention for palliation may have significant clinical relevance. Pain is the most common symptom warranting palliative intervention, usually local irradiation. This may be augmented through systemic therapy (chemotherapy or hormonal therapy) when bony/visceral metastases are present. Less commonly, prophylactic therapeutic intervention may be advised in the absence of symptoms. The best example of this recommendation is the asymptomatic weight bearing skeletal metastasis. In an effort to prevent a future pathologic fracture, with its attendant effect on quality of life, it is wise to treat such metastases prophylactically.

TABLE 38.3 *Breast cancer management guidelines*

TNM	Surgery	Radiation	Chemotherapy/Hormonal Therapy			
			Receptors[a] Absent		Receptors[b] Present	
			Pre	Post	Pre	Post
Tis N0 M0	Lump vs TM	Breast (for diameter between 2 and 5 cm)	/	/	/	/
T1 N0 M0	Lump/Ax vs MRM	Breast for Lump/Ax	+/	+/+	+/+	/+
T0 N1 M0	AX vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T1 N1 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T2 N0 M0	Lump/Ax vs MRM	Breast	+/	+/+	+/+	+/+
T2 N1 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T3 N0 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T0 N2 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T1 N2 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T2 N2 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T3 N1 M0	Lump[b]/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T3 N2 M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
T4 Any N M0	Lump/Ax vs MRM	Breast, SCF, CW	+/	+/+	+/+	+/+
Any T N3 M0	Lump vs TM	Breast, AX, SCF, CW, IMN	+/	+/+	+/+	+/+
Any T Any N M1 (SCF)	Lump vs TM	Breast, AX, SCF, CW, IMN	+/	+/+	+/+	+/+
Any T Any N M2 (all other)	Lump vs TM	Symptomatic site (any) and/or asymptomatic weight bearing bone	+/	+/+	+/+	+/+

Abbreviations: Pre, premenopausal; Post, postmenopausal; Lump, lumpectomy; TM, total mastectomy for tumor diameter >5 cm; Lump/Ax, lumpectomy and axillary lymph node dissection; AX, axillary nodes; MRM, modified radical mastectomy; SCF, supraclavicular fossa (for T3 or T4 lesions and/or >4 axillary nodes involved; CW, chest wall when >4 axillary nodes involved; IMN, internal mammary nodes.

[a]Estrogen and progesterone receptors (+, present; –, absent).

[b]Provided primary tumor mass can be excised with clear margins and without disturbing the cosmetic appearance of the breast.

Having established a sarcoma diagnosis through open biopsy (FNA is unreliable in sarcomas), the local tumor undergoes wide excision that may require total mastectomy when wide excision would cosmetically alter the breast. Since lymphatic spread is unusual, axillary lymph node dissection is performed for clinical axillary lymph node involvement only. When total mastectomy is not required, the remaining breast should be irradiated in the early postoperative period. Chemotherapy remains investigational at this time. For established pulmonary metastasis, pulmonary metastectomy is advised, as up to 20% of patients with resectable metastases can be cured.

Total mastectomy and axillary lymph node dissection is advocated for large primary lymphomas of the breast. Recurrent local disease and accessible regional disease should be managed with radiotherapy, and systemic or multiregional disease with chemotherapy using current regimens for non-Hodgkin's lymphoma.

KEY POINTS

- Having established diagnosis of breast cancer, accurate staging is necessary for treatment selection, prognosis, and outcome comparisons
- When lumpectomy is followed by breast irradiation, local control and survival are equivalent to mastectomy
- It is common practice to advise adjuvant systemic treatment, which has improved survival in patients with node-negative and node-positive breast cancer

FOLLOW-UP

Similar to breast cancer surveillance and metastatic evaluation (at initial diagnosis), breast cancer recurrence surveillance requires the knowledge of body sites at risk of recurrent/progressive disease. The frequency of surveillance follows our knowledge of time interval to recurrence. As previously discussed, lung, bone, and liver are the more common sites of systemic disease. Axillary and supraclavicular fossa lymph nodes are the more common sites of regional disease. The breast (in patients locally treated with breast preservation) and chest wall (in patients locally treated with mastectomy) are common sites of local recurrence. Therefore, anatomic sites of recur-

PATIENT _____ Hospital # _____

	PREOP	3MO	6MO	9MO	1YR	15MO	18MO	21MO	2YR	2.5YR	3YR	3.5YR	4YR	4.5YR	5YR[2]
PHYS EXAM															
MAMMO															
CXR															
LFTs & CBC															
BONE SCAN[1]															
OTHER															

[1]For T3 lesions, new bone pain, elevated alkaline phoshatase @ pre-op or recent elevation during follow-up.
[2]Annual follow-up, only, beyond five years. Continue annual follow-up for life of patient.

STAGE	THERAPY	RECURRENCE
T _____ N _____ M _____ If Node Positive, ?/? nodes are +. ___ / ___ SITE _____	OPERATION _____ _____ DATE _____	SITE _____ DATE _____
HISTOLOGY:	RADIATION: (circle one) YES NO	RESTAGING:
RECEPTORS: (circle one) ER positive negative PR positive negative	CHEMOTHERAPY: (circle one) YES NO	TREATMENT:
	HORMONAL THERAPY: (circle one) YES NO	

FIGURE 38.1 *Harbor/University of California at Los Angeles, follow-up regimen for breast cancer patients.*

rence surveillance include bilateral supraclavicular fossa, breast/chest wall, bilateral axillae, bone, and liver. The modalities for surveillance include history/alkaline phosphatase (bone), palpation (supraclavicular fossa), auscultation/chest x-ray (chest), palpation (axilla), palpation/mammography (breast, chest wall), and palpation/liver function tests (liver). Recurrence risk is greatest within the initial 5 years and continues for as long as 20 years, reflected in the frequency of recurrence surveillance (Fig. 38.1).

Recurrence sites for mammary sarcomas and lymphomas are pulmonary (local) and multiple bony and visceral sites, including bone marrow (local/regional) respectively. With one exception, these body sites should be surveyed in a manner similar to that of mammary carcinoma. In the presence of a diagnosis of mammary sarcoma, compared tomography (CT) scans of the chest should be performed when radiography is negative and mastectomy is planned.

SUGGESTED READINGS

Devita VT, Hellman S, Rosenberg SA: Cancer: Principles and Practice Oncology. Lippincott-Raven, Philadelphia, 1993

Comprehensive multidisciplined oncology text (weakest discipline is surgery).

Donegan WL, Spratt JS: Cancer of the Breast. WB Saunders, Philadelphia, 1995

Comprehensive breast cancer text (strong surgical presence).

Early Breast Cancer Trialist Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 39:8784, 1992

Overview analysis of systemic breast cancer treatment. Highly technical process yet simplified end product (treatment algorithm).

QUESTIONS

1. Breast cancer screening includes?

A. Breast self-examination.
B. Breast ultrasonography.
C. FNA of a suspicious breast mass.
D. Mammography obtained in a 35-year-old patient with a self-discovered lump.

2. Staging of breast cancer may include?

A. Physical examination.
B. CT scan of the liver.
C. Axillary node dissection.
D. Serum alkaline phosphatase.
E. All of the above.

(See p. 604 for answers.)