

2. BREAST CANCER DIAGNOSIS AND TREATMENT¹

Deidre Gifford MD, MPH and Lisa Schmidt, MPH

The literature for this chapter was identified by a MEDLINE search of English language review articles from 1992 to the present on the subjects of breast mass, breast cancer treatment, and breast cancer follow-up. Consensus statements and guidelines on the subject were also reviewed, after which topics for indicators were developed. Randomized trials and meta-analyses pertinent to the indicators were then examined to verify the information contained in the reviews and to finalize the indicators. The topic of screening for breast cancer is covered in Chapter 1.

IMPORTANCE

See Chapter 1 for a discussion of the importance of breast cancer.

DIAGNOSIS

Clinical examination of the breast can detect a mass, but it is not sufficient to distinguish a benign from a malignant process (Donegan, 1992). Although characteristics such as indistinct borders, skin dimpling, or nipple retraction may distinguish breast cancer from a benign mass, the absence of these characteristics cannot reliably differentiate a benign mass from a malignant tumor. In addition, a clinical exam cannot distinguish a cystic from a solid breast mass (Donegan, 1992).

The American College of Obstetricians and Gynecologists (ACOG) recommends that all positive findings from a breast examination be documented in writing or with an appropriate drawing in the patient's chart (ACOG, 1991). In addition, a comprehensive history, including age, menstrual status, parity, previous history of breast-feeding, family medical history, and drug usage should be noted (Bland and Love, 1992).

Some type of follow-up should be provided for all women with a breast mass detected by physical examination (Indicator 1). Bland and Love (1992)

¹ This chapter is a revision of one written for an earlier project on quality of care for women and children (Q1). The expert panel for the current project was asked to review all of the indicators, but only rated new or revised indicators.

and Dixon and Mansel (1994) recommend fine needle aspiration (FNA) for any palpable breast mass (Indicator 2). Cytologic examination and FNA have been shown to be efficacious, cost-effective, and highly reliable when cytologic preparation and cellular sampling are properly done (Bland and Love, 1992) (Indicator 3). Aspiration is also effective for differentiating a cyst from a solid mass (Donegan, 1992). If the FNA cannot rule out breast cancer, an open biopsy should be performed (ACOG, 1994) (Indicator 4). In addition, ACOG (1991) suggests that any of the following findings on FNA requires that an open biopsy be performed:

- Bloody cyst fluid on aspiration;
- Failure of mass to disappear completely upon fluid aspiration;
- Recurrence of cyst after one or two aspirations;
- Solid dominant mass not diagnosed as fibroadenoma;
- Bloody nipple discharge;
- Nipple ulceration or persistent crusting; or
- Skin edema and erythema suggestive of inflammatory breast carcinoma.

Mammography is an essential part of the examination of a palpable breast mass (ACOG, 1994; Donegan, 1992). Significant mammographic findings are alterations in breast tissue density, calcifications, skin thickening, fibrous streaks, and nipple discharge (ACOG, 1991). However, mammography alone is not sufficient to rule out malignant pathology. Ultrasonography or magnified mammographic imaging of the breast may provide additional information and identify cysts or variations in normal breast architecture that account for the palpable abnormality (ACOG, 1994). Sonograms cannot distinguish benign from malignant masses, although they can accurately identify masses as cystic or solid (Donegan, 1992) (Indicator 3b). Sonograms are most helpful when a mass cannot be felt, when the patient will not permit aspiration, or when a mass is too small and deep to offer a reliable target for aspiration (Donegan, 1992).

The combination of physical examination, mammography, and FNA is highly accurate when all the tests give the same results (Donegan, 1992). A study discussed by Donegan (1992) found cancer in only three of 457 cases in which all three evaluations indicated that a mass was benign.

TREATMENT

The principal treatment for breast cancer in this century has been radical mastectomy. Breast cancer was believed to be a local/regional disease process that was best treated by aggressive local excision. More recently, treatment has moved toward a more conservative surgical approach, with adjuvant systemic therapy for women with evidence of spread of the disease to regional lymph nodes (Hortobagyi and Buzdar, 1995; National Institutes of Health, 1990).

Clinical staging of breast cancer uses the Tumor, Nodes, Metastases (TNM) system. This process assesses the tumor size, level of lymph node involvement, and presence or absence of metastases. Tables 2.1 and 2.2 show the definitions used for breast cancer staging.

Table 2.1
Definitions for Breast Cancer Staging

Tumor	
TIS	Carcinoma in situ (intraductal carcinoma, lobular)
T0	No evidence of primary tumor
T1	Tumor \leq 2cm in greatest dimension
T2	Tumor > 2cm but \leq 5cm in greatest dimension
T3	Tumor > 5cm in greatest dimension
T4	Tumor of any size with direct extension into chest wall or skin
Nodes	
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral axillary node(s)
N2	Metastases to ipsilateral axillary lymph node(s), fixed to one another or other structures
N3	Metastases to ipsilateral internal mammary lymph nodes
Metastases	
M0	No distant metastases
M1	Distant metastases including ipsilateral supraclavicular nodes

Source: Adapted from Philips and Balducci (1996)

Table 2.2
Classification of Breast Cancer Stages

Stage 0:	TIS N0 M0
Stage I:	T1 N0 M0
Stage IIA:	T0 N1 M0, T1 N1 M0, T2 N0 M0
Stage IIB:	T2 N1 M0, T3 N0 M0
Stage IIIA:	T0 N2 M0, T1 N2 M0, T2 N2 M0, T3 N1/2 M0
Stage IIIB:	T4, any N, M0; or any T, N3
Stage IV:	Any T, any N, M1

Source: Adapted from Philips and Balducci (1996)

Surgical Treatment

In 1990, a National Institutes of Health (NIH) consensus panel reviewed the surgical treatment of early stage breast cancer (Stages I and II). In 1992, a consensus statement by four professional societies -- the American College of Radiology, American College of Surgeons, College of American Pathologists and Society of Surgical Oncology -- reviewed the literature and

concluded that breast-conserving surgery is a reasonable option for women with Stage I or II breast cancer. This conclusion was based on the results of seven randomized controlled trials with up to 17 years of follow-up comparing mastectomy with breast-conservation treatment in conjunction with whole breast irradiation. Breast conservation is defined as the excision of the primary breast tumor and adjacent breast tissue (breast-conserving surgery) and the dissection of ipsilateral lymph nodes, followed by irradiation. Breast-conserving surgery is also commonly referred to as lumpectomy, partial mastectomy, and segmental mastectomy (Winchester, 1992). Modified radical mastectomy involves removal of the entire breast with dissection of ipsilateral lymph nodes. All seven trials found that relapse-free survival and overall survival for both breast conservation and mastectomy were the same. From these results, the NIH consensus and the professional society consensus concluded that primary treatment for Stage I or II breast cancer can include *either* modified radical mastectomy *or* breast conservation treatment (Indicator 5). According to the NIH, no subgroups have been identified in which radiation therapy can be avoided after breast-conserving surgery (Indicators 6 and 7).

According to the NIH consensus, important considerations in the choice of surgical therapy for women with Stage I or II breast cancer include factors that influence local/regional tumor control, cosmetic results, psychosocial issues, and patient preferences for treatment method. Women with multicentric breast malignancies, including those with gross multifocal disease or diffuse microcalcifications detected by mammography, were believed to be inappropriate candidates for breast-conserving treatment, as were women for whom "breast conservation treatment would produce an unacceptable cosmetic result (e.g., women with large tumors relative to breast size and those with certain collagen vascular diseases)." In all other cases, the NIH suggests that "women should be educated about treatment choices and clinical trial options in order to make an informed decision in consultation with their physicians. A woman's body image and her beliefs and concerns may determine her preference for breast conservation treatment or mastectomy." In keeping with this recommendation of the NIH, the professional society consensus states that an assessment of the patient's needs and expectations is critical in patient selection for breast conservation treatment, as are a history and physical exam, mammography, and histologic assessment of the resected breast specimen (Winchester, 1992).

Adjuvant Systemic Therapy

In the 1970s, randomized clinical trials began to examine the benefits of adjuvant systemic therapy for women with early stage breast cancer. Early trials demonstrated that 1) adjuvant chemotherapy improved disease-free and overall survival; 2) adjuvant tamoxifen improved disease-free and overall survival; and 3) ovarian ablation prolonged disease-free and, sometimes, overall survival for premenopausal women (Hortobagyi and Buzdar, 1995). In 1985, and again in 1990, the Early Breast Cancer Trialists Collaborative Group (EBCTCG) performed a meta-analysis of all available randomized trials of adjuvant systemic therapy in early stage breast cancer begun before 1985. They pooled the results of 133 studies involving 75,000 women, which provided greater statistical power than individual studies to examine results (EBCTCG, 1992). This meta-analysis established that adjuvant chemotherapy or adjuvant tamoxifen produced significant reductions in the annual odds of recurrence and the annual odds of death compared with no adjuvant systemic treatment. It also confirmed that combination chemotherapy was superior to single-agent chemotherapy (EBCTCG, 1992; Hortobagyi and Buzdar, 1995).

Tamoxifen

Results of the EBCTCG meta-analysis showed reductions of 25 percent in the annual odds of recurrence and 17 percent in the annual odds of death for all women treated with tamoxifen. Both of these findings were statistically significant ($p < 0.00001$). Ten year recurrence-free survival was 51 percent in the tamoxifen groups and 44 percent in controls ($p < 0.00001$). Overall survival at ten years was 59 percent in the tamoxifen groups and 53 percent in the controls ($p < 0.00001$). When the results were stratified by age, the analysis showed that the reduction in the odds of death occurred only for women over 50 years old, while the reduction in recurrence was seen in all age groups. This result, however, should be interpreted with caution, because the number of women in the tamoxifen trials below the age of 50 was smaller than the number of women over age 50 (8,612 vs. 21,280). The proportional risk reductions for both overall survival and recurrence-free survival were the same in node-negative and node-positive women, but because recurrence is generally more common in node-positive women, the absolute reduction in recurrence and death is greater in the node-positive group (Indicator 7). The EBCTG found a greater increase in recurrence-free survival in those trials which used \geq two years of Tamoxifen compared to those which used less than two years (Indicator

7). Randomized trials are currently underway to study the optimal duration of Tamoxifen therapy (Current Trials Working Party of the Cancer Research Campaign Breast Cancer Trials Group, 1996).

Combination Chemotherapy

The EBCTCG overview reported the results of 31 randomized trials that included 11,000 women undergoing long-term (greater than two months) combination chemotherapy versus no chemotherapy. The median duration of treatment in these trials was 12 months. Five year recurrence-free survival was 59 percent in the chemotherapy groups versus 50 percent in the no chemotherapy group, a statistically significant reduction in recurrence of nine percent at five years. This difference persisted, but did not increase at ten year follow-up. Ten year overall survival in the chemotherapy group was 51 percent vs. 45 percent in the no chemotherapy group, again a statistically significant reduction in deaths for the chemotherapy group. When stratified by nodal status, the recurrence-free survival was increased by nearly nine percent in node-positive women, and by seven percent in node-negative women. Overall survival at ten years was better by seven percent for node-positive women, and by four percent for node-negative women. All improvements in outcome for both node-positive and node-negative women were statistically significant (Indicator 7).

Ovarian Ablation

Results are available for 12 trials involving 3,000 women comparing ovarian ablation with no ablation. After 15 years, 53 percent of ovarian ablation patients and 42 percent of controls were alive and free of recurrence, for a statistically significant difference between groups of 11 percent. Among the 1,326 women over the age of 50, there was no significant effect of ovarian ablation on recurrence-free survival or overall survival. The effects in women under the age of 50 were highly statistically significant. For these women, as seen in the other analyses, the magnitude of the absolute benefit is likely to depend on nodal status. Among node-positive women less than 50 years old, the increases in recurrence-free survival (11%) and overall survival (13%) were significant. For node-negative women less than 50 years old, the number that died or had a recurrence was smaller, so the effects of treatment are not as reliably known.

Summary of Adjuvant Treatment

Both tamoxifen and combination chemotherapy have been shown to produce statistically significant increases in survival in all women with breast cancer. Ovarian ablation produces statistically significant reductions in recurrence and mortality in women under the age of 50.

The absolute reductions in recurrence and mortality are greatest in women with node-positive disease, since the absolute risk of recurrence or death is greatest in this group. However, some reduction in recurrence and death can also be expected in women with node-negative disease. In these women, since the absolute risk of recurrence is small, the risk/benefit ratio of adjuvant systemic treatment needs to be considered (NIH Consensus, 1990). Among women with node negative disease, characteristics such as overall health and menopausal status, and indicators of prognosis such as tumor size and nuclear grade may be used to inform the choice of adjuvant therapy.

FOLLOW-UP

In the past, intensive follow-up of women after primary treatment for breast cancer was recommended. Such follow-up often included the use of bone scans, chest x-rays, liver sonograms and other imaging, and was felt to lead to earlier detection of recurrence and improved survival. Recently, consensus has developed that intensive follow-up with radiologic testing may lead to earlier detection of recurrence in some cases, but does not improve overall survival or quality of life (Consensus Conference, 1995). A randomized trial of 1,320 women treated for primary breast cancer compared clinical exam and annual mammography to clinical exam and annual mammography plus bone scans, liver sonograms, and chest X-rays at regular intervals (GIVIO Investigators, 1994). This study showed no difference in overall survival, time to detection of recurrence, or health-related quality of life between the two groups after a median follow-up of 71 months. Annual mammography is indicated to detect new primary cancers in the contralateral breast or recurrence in the ipsilateral breast after breast-conserving surgery (Consensus Conference, 1995) (Indicators 8 and 9). Periodic provider visits and clinical breast exam are indicated to detect signs and symptoms which would direct further diagnostic testing (Indicators 9 and 10).

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RECOMMENDED QUALITY INDICATORS FOR BREAST CANCER DIAGNOSIS AND TREATMENT

The following criteria apply to women age 18 and older. Only the indicators in bold type were rated by this panel; the remaining indicators were endorsed by a prior panel.

Indicator	Quality of Evidence	Literature	Benefits	Comments
Diagnosis				
1. If a palpable breast mass has been detected, at least one of the following procedures should be completed within 3 months: <ul style="list-style-type: none"> • Fine needle aspiration; • Mammography; • Ultrasound; • Biopsy; • Follow-up visit. 	III	ACOG, 1991; ACOG, 1994; Bland & Love, 1992; Dixon & Mansel, 1994	Reduce late-stage breast cancer. Decrease mortality from breast cancer.	Any breast mass may be an indicator of cancer and needs to be followed closely and/or investigated further. The 3-month time period is not specified in the literature but is probably generous. The modality of follow-up may differ depending on the patient and mass characteristics.
2. If a breast mass has been detected on two separate occasions, then either a biopsy, FNA or ultrasound should be performed within 3 months of the second visit.	III	ACOG, 1991; ACOG, 1994; Bland & Love, 1992; Dixon & Mansel, 1994	Reduce late-stage breast cancer. Decrease mortality from breast cancer.	A definite mass (as opposed to fibrocystic changes) needs further work-up. Although a follow-up visit to determine change in nature or size with menstrual cycle may be appropriate one time, a biopsy or FNA for diagnosis needs to occur if a definite mass is palpated twice. The time frame is debatable.
3. A biopsy or FNA should be performed within 6 weeks of either of the following circumstances: <ol style="list-style-type: none"> a. Mammography suggests malignancy;¹ b. Persistent palpable mass is not cystic on ultrasound. 	III	ACOG, 1991	Reduce late-stage breast cancer. Decrease mortality from breast cancer.	Mammographic signs of malignancy or persistent solid mass require cytologic or histologic diagnosis to rule out malignancy.
4. A biopsy should be performed within 6 weeks if FNA cannot rule out malignancy. ²	III	ACOG, 1994	Reduce late-stage breast cancer. Decrease mortality from breast cancer.	Histologic confirmation of the diagnosis is required if FNA of a solid mass is suspicious or non-diagnostic.

Indicator	Quality of Evidence	Literature	Benefits	Comments
Treatment				
5. Women with Stage I or Stage II breast cancer should be offered a choice of modified radical mastectomy or breast-conserving surgery, unless contraindications to breast-conserving surgery ³ are present.	I	NIH, 1990; Winchester, 1992	Allow women the option of breast preservation while reducing mortality from breast cancer.	Breast-conserving surgery and modified radical mastectomy have equivalent survival outcomes.
6. Women treated with breast conserving surgery should begin radiation therapy within 6 weeks of completing either of the following (unless wound complications prevent the initiation of treatment): <ul style="list-style-type: none"> • last surgical procedure on the breast (including reconstructive surgery); or • chemotherapy, if patient receives adjuvant chemotherapy. 	III	NIH, 1990; EBCTCG, 1992; Winchester, 1992	Reduce recurrence and mortality from breast cancer. Obtain maximum benefit from radiation therapy.	Although there may be a subset of women who do not benefit from radiation, current data do not allow identification of any subgroup in which radiation therapy can be avoided. Consensus states that radiation can begin as soon as the patient has healed adequately from the surgical procedure, usually within 2 to 4 weeks.
7. Women over age 50 with node-positive breast cancer should be treated with adjuvant systemic therapy to include one of the following: <ul style="list-style-type: none"> • Combination chemotherapy (more than one agent, lasting for at least 2 months); • Tamoxifen (20 mg/d for at least 2 years). 	I	EBCTCG, 1992	Reduce recurrence and mortality from breast cancer.	Although adjuvant therapy has been shown to reduce recurrence and mortality in both node-positive and node-negative cases, the absolute risk of recurrence is smaller in node-negative cancer.

Indicator	Quality of Evidence	Literature	Benefits	Comments
Follow-up				
8. Women with a history of breast cancer should have yearly mammography.	I	Consensus Conference, 1995; Givio, 1994	Detect recurrent or new primary breast cancers.	Yearly mammography and regular clinical exam have been shown to lead to equivalent survival and quality of life as more intensive follow-up programs.
9. Women diagnosed with breast cancer in the past 5 years should have a clinical breast exam in the past 6 months.	III	Winchester, 1992	Detect signs and symptoms of recurrence.	Signs and symptoms of recurrence detected during clinical exams should guide the use of ancillary diagnostic tests.
10. Women diagnosed with breast cancer more than 5 years ago should have a clinical breast exam in the past year.	III	Winchester, 1992	Detect signs and symptoms of recurrence.	Signs and symptoms of recurrence detected during clinical exams should guide the use of ancillary diagnostic tests.

Definitions and Examples

¹ Mammography suggests malignancy: Any mammogram in which the result reads “suggestive of malignancy, cannot rule out malignancy, or suspicious calcifications.”

² FNA cannot rule out malignancy: Any pathology report except one which reads “fibroadenoma.” This would include those that have insufficient tissue or normal breast tissue, because of the likelihood that the FNA may have missed the lesion.

³ Contraindications to breast-conserving surgery: These include multicentric breast malignancies, large tumors relative to breast size, pathologic features of the tumor and certain collagen vascular diseases. Because of the subjective nature of this determination, any statement that breast conserving surgery is contraindicated will be accepted.

Quality of Evidence Codes

- I RCT
- II-1 Nonrandomized controlled trials
- II-2 Cohort or case analysis
- II-3 Multiple time series
- III Opinions or descriptive studies