Treatment of Breast Cancer

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Understanding breast cancer treatment options can help family physicians care for their patients during and after cancer treatment. This article reviews typical treatments based on stage, histology, and biomarkers. Lobular carcinoma in situ does not require treatment. Ductal carcinoma in situ can progress to invasive cancer and is treated with breast-conserving surgery and radiation therapy without further lymph node exploration or systemic therapy. Stages I and II breast cancers are usually treated with breast-conserving surgery and radiation therapy. Radiation therapy following breast-conserving surgery decreases mortality and recurrence. Sentinel lymph node biopsy is considered for most breast cancers with clinically negative axillary lymph nodes, and it does not have the adverse effects of arm swelling and pain that are associated with axillary lymph node dissection. Choice of adjuvant systemic therapy depends on lymph node involvement, hormone receptor status, ERBB2 (formerly HER2 or HER2/neu) overexpression, and patient age and menopausal status. In general, node-positive breast cancer is treated systemically with chemotherapy, endocrine therapy (for hormone receptor–positive cancer), and trastuzumab (for cancer overexpressing ERBB2). Anthracycline- and taxane-containing chemotherapeutic regimens are active against breast cancer. Stage III breast cancer typically requires induction chemotherapy to downsize the tumor to facilitate breast-conserving surgery. Inflammatory breast cancer, although considered stage III, is aggressive and requires induction chemotherapy followed by mastectomy, rather than breast-conserving surgery, as well as axillary lymph node dissection and chest wall radiation. Prognosis is poor in women with recurrent or metastatic (stage IV) breast cancer, and treatment options must balance benefits in length of life and reduced pain against harms from treatment. (*Am Fam Physician.* 2010;81(11):1339-1346. Copyright © 2010 American Academy of Family Physicians.)

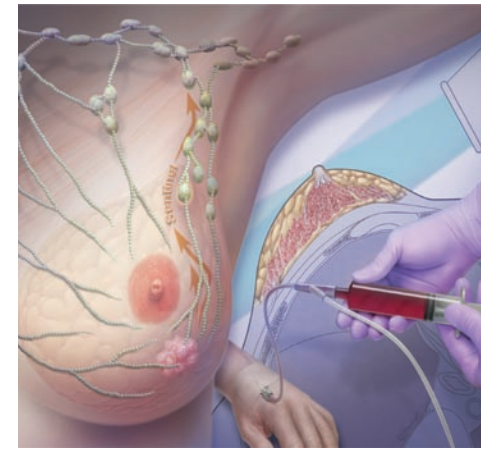

ILLUSTRATION BY SCOTT BODELL

▶ **See related editorial on page 1330.**

▶ **Patient information:** A handout on breast cancer treatment, written by the authors of this article, is provided on page 1347.

Breast cancer is the second most common cause of cancer mortality in women in the United States.[1] One in eight women will be diagnosed in her lifetime.[2] Breast cancer treatments continue to evolve, and although family physicians do not generally make primary decisions about these therapies, understanding their rationale and underlying evidence can help with the care of their patients during and after cancer treatment. *Table 1* lists the five-year survival prognosis for each stage of breast cancer.[3,4]

Breast cancer prognosis and treatment options are generally based on tumor-node-metastasis staging.[5] Lymphovascular spread, histologic grade, hormone receptor status, ERBB2 (formerly HER2 or HER2/neu) overexpression, comorbidities, and patient menopausal status and age are also important factors. *Table 2* outlines typical treatment options by cancer stage and type.[6-22]

Stage 0: In Situ

Lobular carcinoma in situ is an incidental microscopic finding of abnormal tissue growth in the lobules of the breast. It does not progress to, but increases the risk of, subsequent invasive breast cancer in either breast by approximately 7 percent over 10 years.[23] Local and systemic therapies are not indicated, but affected women should undergo rigorous breast cancer surveillance. The National Comprehensive Cancer Network recommends annual mammography and clinical breast examination every six months.[24] Patients should be offered information about chemoprevention with selective estrogen receptor modulators (SERMs), such as tamoxifen.[6]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Breast-conserving surgery should be followed by radiation therapy in women with early-stage invasive or locally advanced breast cancer.	A	8
Sentinel lymph node biopsy results in fewer arm complications compared with axillary lymph node dissection in the treatment of breast cancer.	A	9-11, 20
Axillary lymph node dissection should be performed in women who have breast cancer with clinically palpable lymph nodes.	C	32
Aromatase inhibitors, with or without tamoxifen, should be offered to all postmenopausal women with hormone receptor–positive breast cancer.	A	12, 38, 40, 51-53
Chemotherapy should be offered to all women who have breast cancer with positive lymph nodes.	C	47
Trastuzumab (Herceptin) should be offered to all women with breast cancer that is overexpressing ERBB2.	A	13, 14
Preoperative chemotherapy for locally advanced breast cancer increases the success of breast-conserving surgery.	A	16, 21

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Conversely, ductal carcinoma in situ (DCIS) can progress to invasive breast cancer. Breast-conserving surgery followed by radiation therapy is standard treatment for DCIS; however, mastectomy may be recommended for extensive or multifocal disease. Pathologic lymph node evaluation is not usually performed because nodal metastasis is rare. There is conflicting evidence regarding endocrine therapy with tamoxifen in women with DCIS.[25,26] Given the risks of tamoxifen and the low risk of recurrence of DCIS, routine use of tamoxifen in women with DCIS is not recommended.

Stages I and II: Early-Stage Invasive

SURGERY

Modified radical mastectomy has traditionally been the standard of care for early-stage invasive breast cancers. However, breast-conserving surgery has been favored more recently. This therapy involves removing the tumor without removing excess healthy breast tissue, with the outcome of a breast that is more aesthetically acceptable to the patient than the outcome from radical mastectomy. Radiation therapy following breast-conserving surgery decreases local recurrence and improves cancer-specific survival rates to rates equivalent to those with mastectomy.[8] Breast-conserving surgery has the highest success rate in women with early-stage breast cancer, but it is not recommended for women at high risk of local recurrence.[27] *Table 3* lists qualifications for consideration of breast-conserving surgery.[7] Women with early-stage breast cancer may opt for mastectomy because of contraindications to radiation therapy or because of personal preference.

EVALUATION OF REGIONAL LYMPH NODES

The status of axillary lymph nodes (ALNs) determines the need for radiation therapy and adjuvant systemic therapy. ALN dissection at the time of surgery was standard care until the 1990s, but often resulted in pain, numbness, swelling, and decreased mobility in the affected arm. In patients with clinically negative nodes, a negative intraoperative sentinel lymph node (SLN) biopsy precludes the need for ALN dissection.

Table 1. Breast Cancer Five-Year Survival by Stage at Diagnosis

Cancer stage	*Classification*	*Five-year survival rate (percent)*
0	In situ	100*[3]
I, IIa, IIb	Early invasive	98.0 (local)*[3]
		83.6 (regional)*[3]
IIIa, IIIb, IIIc	Locally advanced†	57[4]
IV	Metastatic†	23.4*[3]

NOTE: *Definitions for classifying breast cancers by tumor-node-metastasis stage are available at http://www.cancer.gov/cancertopics/pdq/treatment/breast/HealthProfessional/page4#Section_30.*

**—Data were collected through 2006 and reported using classifications of in situ, localized, regional, and distant. Current language uses classifications of in situ, early invasive, locally advanced, and metastatic. Interpretation of survival data must take into consideration that treatment and terminology have changed over time.*

†—Inflammatory breast cancer may be stage IIIb, IIIc, or IV.

Information from references 3 and 4.

Table 2. Typical Treatment Options for Breast Cancer by Stage

Cancer stage and type	*Primary treatment*	*Node evaluation*	*Adjuvant therapy*		
			Hormone receptor negative	*Hormone receptor positive*	*ERBB2 overexpression*
Stage 0: in situ					
Lobular carcinoma in situ	No treatment or consider prophylaxis with tamoxifen[6]	—	—	—	—
Ductal carcinoma in situ	Breast-conserving surgery (consider mastectomy if extensive or multifocal) and radiation therapy	—	—	—	—
Stages I and II: early-stage invasive	Breast-conserving surgery[7] and radiation therapy[8]	SLN biopsy[9-11] or ALN dissection*	Chemotherapy†	Chemotherapy and endocrine therapy[12]	Chemotherapy and trastuzumab (Herceptin)[13,14]
Stage III: locally advanced					
Noninflammatory	Induction chemotherapy,[15] followed by breast-conserving surgery‡[16-19] and radiation therapy	ALN dissection or SLN biopsy[20]	Induction chemotherapy[15,21]	Induction chemotherapy and postoperative endocrine therapy	Induction chemotherapy and postoperative trastuzumab
Inflammatory	Induction chemotherapy, followed by mastectomy and radiation therapy	ALN dissection			
Stage IV: metastatic					
Initial or recurrent	Address patient's treatment goals; radiation therapy or bisphosphonates for bone pain	—	Chemotherapy	Endocrine therapy with or without chemotherapy	Trastuzumab with or without chemotherapy
Recurrent					
Local after breast-conserving surgery	Mastectomy	ALN dissection§	Chemotherapy‖	Chemotherapy and endocrine therapy¶	Chemotherapy and trastuzumab
Local after mastectomy	Wide excision	ALN dissection**			
Local inoperable	Induction chemotherapy	ALN dissection			

ALN = axillary lymph node; SLN = sentinel lymph node.

**—SLN biopsy if clinically negative nodes; otherwise, ALN dissection is recommended.*

†—*Except lowest risk (i.e., tumor ≤ 1 cm, node negative).*

‡—*Mastectomy may be considered if tumor does not sufficiently respond to induction chemotherapy.*

§—*If nodes are clinically negative and SLN biopsy is done initially, SLN biopsy can be repeated; if nodes are clinically positive, ALN dissection is needed.*

‖—*Local recurrence is often associated with distant metastases; therefore, prophylactic chemotherapy theoretically may be of benefit and is currently being studied.*[22]

¶—*Benefit of adjuvant therapy is uncertain and currently being studied; until results are available, chemotherapy is generally recommended.*

***—May not need to explore axilla if ALN dissection is done initially and there are clinically negative nodes with recurrence.*

Information from references 6 through 22.

SLN biopsy reduces arm symptoms compared with ALN dissection.[9-11] SLN biopsy has a sensitivity of 95 to 100 percent, a false-negative rate of 5.5 percent,[28] and a negative predictive value of 98 percent.[29,30] A prospective analysis provides evidence that patients with early-stage breast cancer who have a negative SLN have improved disease-free and overall survival compared with patients who have a negative ALN dissection.[31] This is most likely because of more accurate axillary staging in patients from the SLN group. ALN dissection is indicated for all women with palpable lymph nodes or a positive SLN.[32]

Radiation Therapy

Typically, whole-breast radiation is performed following breast-conserving surgery to treat subclinical disease. A review of 10 randomized controlled trials (RCTs) comparing breast-conserving surgery with and without radiation showed that radiation in addition to surgery significantly reduced the five-year local recurrence rate, regardless of the use of adjuvant systemic therapy (7 versus 26 percent; number needed to treat [NNT] = 5), and appeared to decrease the 15-year breast cancer mortality risk (30.5 versus 35.9 percent; NNT = 18).[8]

According to a systematic review of three RCTs, the sequencing of chemotherapy and radiation therapy does not appear to have a major effect on survival or recurrence as long as radiation is commenced within seven months of surgery.[33] Radiation therapy is expensive and time-consuming, and shorter therapies can be appealing. Five-year results appear favorable in studies evaluating brachytherapy and compressed schedules of radiation; however, long-term data are lacking.[34,35]

ADJUVANT SYSTEMIC THERAPIES

Most women with early-stage breast cancer receive adjuvant systemic therapies. Chemotherapy, endocrine therapy, and tissue-targeted therapies enhance definitive local therapy (surgery, radiation therapy, or both), substantially decreasing cancer recurrence and disease-specific death. Node-positive disease benefits most from systemic therapy. *Table 4* outlines the medications typically used with these therapies.[24,36-46]

Chemotherapy. Chemotherapy is the standard of care for women with node-positive cancer or with a tumor larger than 1 cm. Hormone receptor–negative disease derives more benefit from chemotherapy than hormone receptor–positive disease.[47] Factors such as age and comorbidities also influence the decision to use chemotherapy. Most studies suggest a small benefit for treatment with anthracyclines or taxanes over other chemotherapies,[12] particularly in women with tumors overexpressing ERBB2.[48] A systematic review of 12 studies demonstrated

Table 3. Qualifying Factors for Consideration of Breast-Conserving Surgery in the Treatment of Breast Cancer

Localized tumor*
Negative surgical margins
No diffuse (inflammatory) or multicentric cancer
No malignant-appearing mammographic abnormality after surgery
No previous radiation therapy to the breast or chest wall (precludes further radiation therapy)

**—Large tumor size in small breast may preclude the benefit of breast-conserving surgery (relative contraindication).*

Information from reference 7.

Table 4. Medications Used in the Treatment of Breast Cancer

Therapy type	*Medication*	*Typical course of treatment*
Chemotherapy[24]	**Anthracyclines**	
	Doxorubicin (Adriamycin)	IV every 14 to 21 days for four to six cycles; used in combination with a taxane (docetaxel [Taxotere] or paclitaxel [Taxol]), cyclophosphamide, and/or fluorouracil
	Epirubicin (Ellence)	IV day 1 or days 1 and 8, every 21 to 28 days for three to eight cycles; used in combination with cyclophosphamide or fluorouracil
	Taxanes	
	Docetaxel	IV every 21 days for three to four cycles; used in combination with doxorubicin, epirubicin, cyclophosphamide, and/or fluorouracil
	Paclitaxel	IV every seven to 21 days for four to 12 cycles; used in combination with doxorubicin and cyclophosphamide
Endocrine	**Aromatase inhibitors**	
	Anastrozole (Arimidex)	Oral tablet daily for five years; used alone or in sequence with tamoxifen[36,37]
	Exemestane (Aromasin)	Oral tablet daily for at least two to five years; used alone or in sequence with tamoxifen[38,39]
	Letrozole (Femara)	Oral tablet daily for two to five years; used alone or in sequence with tamoxifen[40,41]
	Gonadotropin-releasing hormone agonist	
	Goserelin (Zoladex)	Subcutaneously every one to three months for two years[42,43]
	Selective estrogen receptor modulators	
	Tamoxifen	Oral tablet daily for two to five years; used alone or in sequence with an aromatase inhibitor[36]
Tissue-targeted	**Monoclonal antibody**	
	Trastuzumab (Herceptin)	IV with first dose of chemotherapy regimen and then every one or three weeks to complete one year[44-46]

IV = intravenously.

Information from references 24 and 36 through 46.

disease-free and overall survival advantages when using a taxane-containing regimen for premenopausal and postmenopausal women with early-stage breast cancer.[49] A meta-analysis of 13 RCTs determined that adding a taxane to an anthracycline-based regimen improved disease-free survival (five-year risk reduction = 5 percent) and overall survival (five-year risk reduction = 3 percent).[50]

Endocrine Therapy. Endocrine therapies, such as SERMs, aromatase inhibitors, and gonadotropin-releasing hormone agonists, prevent estrogen production or block estrogen, thereby preventing stimulation of an estrogen-sensitive tumor. In premenopausal women, ovarian ablation or oophorectomy may be considered. Endocrine therapy is not effective against cancers that are lacking hormone receptors. Five years of treatment with tamoxifen reduces the breast cancer death rate (absolute risk reduction = 9.2 percent over 15 years; NNT = 11).[12]

Aromatase inhibitors should be considered in all postmenopausal women with hormone receptor–positive breast cancer. They block the conversion of androgens to estrogen in postmenopausal women. Trials consistently show that aromatase inhibitors reduce the risk of relapse of early-stage breast cancer both in direct comparison with and after completion of tamoxifen.[36,38,51,52] A large RCT showed that treatment with letrozole (Femara) following five years of treatment with tamoxifen decreased the incidence of contralateral breast cancer and improved disease-specific survival in patients who were node positive.[53] None of these studies showed improvement in overall survival compared with tamoxifen.[36,38,51-53] Many women tolerate aromatase inhibitors better than tamoxifen.[40] Aromatase inhibitors are not indicated for premenopausal women.

Tissue-Targeted Therapy. Approximately 20 to 30 percent of early-stage breast cancers overexpress ERBB2.[44,45] These cancers generally have a worse prognosis. A humanized anti-ERBB2 monoclonal antibody, trastuzumab (Herceptin), improves disease-specific and overall survival when added to anthracyclines and paclitaxel (Taxol) chemotherapy in women with node-positive and high-risk, node-negative breast cancers overexpressing ERBB2.[13,14] The combination of trastuzumab and anthracyclines must be used with caution, however, because cardiac toxicity will develop in 2 to 3 percent of patients over two years of treatment.

Stage III: Locally Advanced

Locally advanced breast cancer (LABC) includes tumors larger than 5 cm, extensive regional lymph node involvement, direct involvement of underlying chest wall or skin, tumors considered inoperable but without distant metastases, and inflammatory breast cancer. Induction chemotherapy followed by local therapy (surgery, radiation therapy, or both) is becoming the standard of care. Five-year survival can be achieved in 55 percent of patients presenting with noninflammatory LABC.[54] The most important prognostic factors are response to induction chemotherapy and lymph node status.

INDUCTION SYSTEMIC THERAPIES

Induction Chemotherapy. Patients with LABC who achieve an excellent response to induction chemotherapy have outcomes similar to those in patients with early-stage disease.[15] Preoperative chemotherapy downsizes the local tumor, facilitating breast-conserving surgery. With induction chemotherapy, 75 percent of patients have a reduction in tumor size greater than 50 percent.[21] Preoperative chemotherapy increases breast conservation rates, but also increases the rate of local recurrence. However, local recurrence is not increased as long as surgery remains part of the treatment, even after complete tumor regression.[21] Mastectomy may be the best option in the case of poor response to induction chemotherapy, or based on patient preference.

Preoperative chemotherapy in locally advanced breast cancer (stage III) downsizes the local tumor, facilitating breast-conserving surgery.

Induction Endocrine Therapy. Induction endocrine therapy (tamoxifen with or without aromatase inhibitors) is less effective than chemotherapy and may be most appropriate for older patients not willing to accept chemotherapy-related toxicity. Patients with hormone receptor–positive LABC are generally best served by combined induction chemotherapy and endocrine therapy following surgery.

Induction Tissue-Targeted Therapy. There are few solid data about the use of tissue-targeted therapy (trastuzumab) as induction therapy. Because of the benefit of adding trastuzumab to adjuvant chemotherapy in early-stage breast cancer, 12 months of postoperative trastuzumab is recommended for patients who have LABC with ERBB2 overexpression.

LOCAL THERAPY

Tumor response to induction chemotherapy determines local therapy, such as surgery (mastectomy or breast-conserving surgery), radiation therapy, or both. Data from uncontrolled prospective studies indicate that 50 to 90 percent of women with LABC can be successfully treated with breast-conserving surgery after

induction chemotherapy, although no RCTs have been completed on this topic.[17,18] In patients whose cancer does not respond to induction chemotherapy, surgery is appropriate only if a complete resection can be attained. Extensive lymph node involvement (i.e., more than three axillary, internal mammary, or clavicular nodes), residual pathologic tumors larger than 2 cm, multifocal residual disease, and lymphovascular invasion increase the rate of local recurrence following breast-conserving surgery after induction chemotherapy and, therefore, warrant mastectomy.[19]

Most patients presenting with LABC have clinically positive lymph nodes and require ALN dissection. In patients with LABC and clinically negative nodes, SLN biopsy following induction chemotherapy has been shown to have a similar detection rate as in early-stage breast cancer without induction chemotherapy.[20] Even in patients who have clinically complete remission with induction chemotherapy, radiation therapy following surgery decreases the local recurrence rate.[55]

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer is relatively rare and is characterized by diffuse erythema and edema (peau d'orange), no palpable mass, early age at diagnosis, poor nuclear grade, negative hormone–receptor status, and poor survival outcome. Management is similar to that of noninflammatory LABC; however, because of the aggressiveness of inflammatory breast cancer, SLN biopsy and breast-conserving surgery are not recommended. After induction chemotherapy, patients are usually treated with mastectomy followed by chest wall radiation.

Stage IV: Metastatic

Some women, including those who relapse after treatment of early-stage breast cancer or LABC, will present with metastatic disease. Five-year survival is attained in only 23.3 percent of these patients[3]; therefore, it is important to understand the patient's treatment goals.

Radiation therapy or bisphosphonates, along with endocrine therapy or chemotherapy, can palliate pain from bony complications. Systemic treatment depends on hormone receptor status, rate of disease progression, and patient willingness to tolerate adverse effects of treatment. Endocrine therapy is generally better tolerated than chemotherapy. In women with rapidly progressive disease, it may be better to treat with chemotherapy, which is more likely to induce a timely response. Trastuzumab with or without chemotherapy is a reasonable choice for the initial treatment of metastatic disease overexpressing ERBB2. Trastuzumab can be used in combination with endocrine therapy for susceptible tumors.

Recurrent Breast Cancer

Following initial treatment, breast cancer can recur locally, regionally (nodes), or at distant metastatic sites. Approximately 11 and 20 percent of patients treated with adjuvant therapies develop locoregional recurrence within five and 10 years, respectively.[56] Locoregional recurrence is an indicator of an aggressive tumor, and early recurrence carries a poor prognosis.[57] Recurrence without clinical metastases has a five-year survival of approximately 40 percent.[22] Mastectomy is indicated for in-breast tumor recurrence after breast-conserving surgery, followed by repeat axillary staging. SLN biopsy is thought to be acceptable if lymph nodes were not removed initially and if there is no clinical evidence of lymph node involvement, although RCTs are lacking.[58,59]

Wide local excision of the recurrent tumor is recommended for an isolated chest wall recurrence. If unresectable, induction chemotherapy may facilitate successful local treatment. If there is evidence of axillary involvement without distant metastases, axillary evaluation is recommended. Radiation therapy is recommended only in the setting of inoperable or incompletely resected recurrent disease. The benefit of adjuvant systemic chemotherapy for patients with recurrence is uncertain,[60] and a large randomized trial is underway.[61] Until results are available, chemotherapy is recommended for recurrent cancer; endocrine therapy is recommend for hormone receptor–positive cancer; and trastuzumab is recommended for tumors overexpressing ERBB2.

New and Upcoming Treatment Options

With the development of gene sequencing, targeted therapies, and molecular diagnostics, breast cancer treatment has the potential to become directed toward each patient's specific tumor characteristics. Estrogen and progesterone receptors are already used to predict a tumor's response to hormone therapy (an example of a prediction of adjuvant therapy benefit is available at http://www.bmj.com/cgi/content-nw/full/337/jul11_2/a540/FIG3), and ERBB2 expression predicts response to treatment with trastuzumab.

Urokinase plasminogen activator and plasminogen activator inhibitor-1 are new prognostic markers. Newly diagnosed breast cancer with low concentrations of these markers has such a low risk of recurrence—especially in patients with hormone receptor–positive tumors receiving adjuvant endocrine therapy—that chemotherapy may provide only minimal benefits.[62]

The Oncotype DX assay measures expression of 21 genes and predicts which patients with node-negative disease are less likely to benefit from chemotherapy.[63] Biomarkers are also being developed to predict severe drug-related toxicity.[63]

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