

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor*

## TREATMENT OF BREAST CANCER

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**B**REAST cancer is a major public health problem worldwide. Management of breast cancer was last reviewed in the *Journal* in 1992.<sup>1</sup> The accumulation of new biologic information, the results of recent clinical trials, and the availability of new diagnostic and therapeutic tools make it appropriate to review the subject again.

## EPIDEMIOLOGY

The incidence of breast cancer in the United States has been increasing gradually for the past three decades.<sup>2,3</sup> It was estimated that 181,600 new cases of breast cancer were diagnosed in the United States in 1997 and that 44,190 people would die of breast cancer during the same year. However, incidence and mortality have recently leveled off and even decreased slightly.<sup>3</sup> Similar decreases in mortality were recently reported in Sweden and the United Kingdom.<sup>4,5</sup>

The incidence of breast cancer increases with age, although the rate of increase slows after menopause.<sup>6,7</sup> Early menarche, late menopause, and nulliparity increase the risk of breast cancer. Atypical lobular or ductal hyperplasia also increases the risk, and benign breast disease does so marginally.<sup>8,9</sup> Other risk factors are early exposure to ionizing radiation, long-term postmenopausal estrogen-replacement therapy, and alcohol consumption. The most important risk factor is a family history of breast cancer.<sup>10-13</sup> About 5 to 10 percent of all breast cancers occur in high-risk families, and there are several familial breast cancer syndromes, including the breast-ovarian cancer syndrome, the Li-Fraumeni syndrome, and Cowden's disease.<sup>12</sup>

## BIOLOGY

The recent identification and cloning of *BRCA1* and *BRCA2* has expanded our knowledge of familial

breast cancer.<sup>14,15</sup> Germ-line mutations in these two genes are associated with a 50 to 85 percent lifetime risk of breast cancer, ovarian cancer, or both. Tests for these mutations exist, and research efforts to develop comprehensive genetic screening and counseling programs are ongoing.<sup>16</sup> All breast cancers have somatic genetic abnormalities. In sporadic breast cancer, abnormalities have been identified in several genes (including *p53*, *bcl-2*, *c-myc*, and *c-myb*),<sup>17,18</sup> and in some cancers normal genes or gene products (*HER-2/neu* and cyclin D1) are overexpressed. However, the number and types of mutations necessary for the development of sporadic breast cancer are not known.

Many factors that stimulate or inhibit growth influence the growth and proliferation of breast-cancer cells.<sup>19</sup> Gonadal steroid hormones (estrogens, progestins, and androgens), growth factors (epidermal growth factor, transforming growth factors  $\alpha$  and  $\beta$ , and insulin-like growth factors I and II), and various cytokines and lymphokines influence the behavior and phenotypic expression of breast cells. For instance, production of parathyroid hormone-related protein, prostaglandin E, or interleukin-6 by the tumor leads to the development of osseous metastases.<sup>20</sup> The recognition that these factors influence the growth and dissemination of breast cancer has provided new targets for therapeutic and preventive intervention.<sup>21-23</sup> Breast cancer also induces neo-vascularization, which, in turn, facilitates the metastatic process.<sup>23</sup> Metastatic spread is not a random mechanical phenomenon but requires systematic interaction among breast cells, stroma, and surrounding normal tissue at both primary and metastatic sites.<sup>24</sup> Adhesion molecules, local mediators, hormones, and growth factors must all act for metastases to develop. On the basis of this new information, diagnosis and treatment have changed. Many new cytotoxic and hormonal agents have emerged from new biologic concepts and are being developed for clinical use.

## DIAGNOSTIC APPROACHES

Systematic screening by means of mammography and clinical examination results in early diagnosis of breast cancer and a 25 to 30 percent decrease in mortality due to breast cancer in women over the age of 50 years (Table 1)<sup>25</sup> and probably also in women between the ages of 40 and 50 years.<sup>26</sup> The American Cancer Society and the National Cancer Institute recommend annual screening mammography for women older than 40 years who have a standard risk of breast cancer.<sup>26,27</sup> In women from high-risk families,

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**TABLE 1. BENEFIT OF SCREENING MAMMOGRAPHY ACCORDING TO AGE.\***

| STUDY                 | DURATION OF FOLLOW-UP | SCREENING INTERVAL | RELATIVE RISK OF DEATH FROM CANCER (95% CI)† |               |
|-----------------------|-----------------------|--------------------|--|---------------|
|                       |                       |                    | AGE 50-74 YR                                 | AGE 40-49 YR  |
|                       |                       |                    | yr   | mo            |
| Edinburgh             | 10                    | 24                 | 0.8 (0.6-1.1)                                | 0.8 (0.5-1.5) |
| Malmö                 | 12                    | 18-24              | 0.9 (0.6-1.2)                                | 0.5 (0.2-1.2) |
| Kopparberg            | 12                    | 24-33              | 0.8 (0.5-0.9)                                | 0.8 (0.4-1.4) |
| Östergötland          | 12                    | 24-33              | 0.8 (0.6-1.0)                                | 1.3 (0.8-2.3) |
| Canada                | 7                     | 12                 | 1.0 (0.6-1.5)                                | 1.4 (0.8-2.2) |
| Health Insurance Plan | 10                    | 12                 | 0.7 (0.5-1.0)                                | 0.8 (0.5-1.2) |
| Stockholm             | 8                     | 28                 | 0.6 (0.4-1.1)                                | 1.0 (0.5-2.0) |
| Gothenburg            | 7                     | 18                 | 0.9 (0.5-1.6)                                | 0.7 (0.3-2.0) |
| Overall               | —                     | —                  | 0.8 (0.7-0.9)                                | 0.9 (0.8-1.1) |

\*Data are modified from Tables 2 and 3 in Kerlikowske et al.,<sup>25</sup> with the permission of the publisher.

†Relative risks are for women who underwent mammographic screening as compared with those who did not. CI denotes confidence interval.

especially those with *BRCA1* or *BRCA2* mutations, screening should start at 25 years of age, or 5 years earlier than the earliest age at which breast cancer was diagnosed in a family member. Substantial technical improvements have been made in screening mammography, and additional improvements are expected to result from digital mammography. Breast magnetic resonance imaging and technetium-99m sestamibi imaging are under evaluation and may further increase our capability for early diagnosis.<sup>28,29</sup>

Twenty years ago, incisional or excisional biopsies were the standard methods for confirming the diagnosis; today, fine-needle aspiration<sup>30</sup> or core needle biopsy<sup>31</sup> is the standard. Ultrasound-guided core needle biopsy, stereotactic biopsy,<sup>32</sup> and magnetic resonance-directed biopsy have become important diagnostic tools, especially for women with suspicious but nonpalpable breast masses. The use of large-core needle-biopsy techniques increases the pathologist's ability to characterize the lesion.<sup>33</sup>

## THERAPY

### Primary Breast Cancer

In some women breast cancer is a local disease without distant spread. Such early breast cancers are usually diagnosed by screening mammography and are highly curable with local or regional treatment alone.<sup>34</sup> However, most women with primary breast cancer have subclinical metastases, and in a high percentage of those treated with apparently curative surgery (with or without radiotherapy), distant metastases ultimately develop.<sup>35,36</sup>

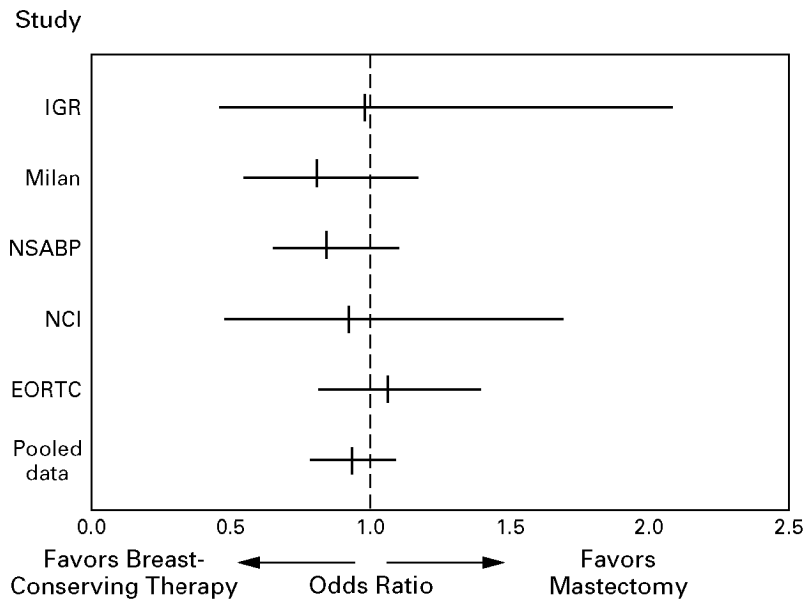
### Local and Regional Treatment

Radical mastectomy has been largely discontinued and is seldom, if ever, indicated today.<sup>37</sup> Randomized trials have established that for most women with early breast cancer, lumpectomy (wide excision of the tumor with preservation of the breast) with radiotherapy is the preferred treatment (Fig. 1),<sup>38</sup> and up to 50 percent of women with early breast cancer in the United States are now treated in this way. However, there are marked geographic variations in the use of this treatment in the United States,<sup>39</sup> suggesting that patients' preferences and physicians' choices often override medical criteria in the selection of treatment. Radiotherapy, an integral part of breast-conserving treatment, is inappropriately withheld from some women, especially those older than 65 years.<sup>40</sup> Noninvasive (in situ) ductal and lobular breast cancer can also be treated adequately with lumpectomy and radiotherapy.<sup>41,42</sup>

### Axillary Lymph-Node Dissection

The probability of recurrence is higher for women with histologically positive axillary lymph nodes and increases with each additional positive node. Axillary lymph-node dissection provides prognostic information but has minimal therapeutic benefit or none, especially in women with clinically negative axillary lymph nodes,<sup>43</sup> and it is responsible for most of the morbidity associated with breast surgery. Therefore, there is increasing interest in developing alternative methods to obtain prognostic information. Sentinel-lymph-node mapping is a procedure in which a radioactive substance or a blue dye is injected into the area around the tumor; a short time later, the lower ipsilateral axilla is explored through a small incision and the lymph node that has taken up the dye or radioactive substance (i.e., the sentinel node) is excised.<sup>44</sup> If it is histologically negative, the rest of the axillary lymph nodes are also likely to be negative. In expert hands, this procedure identifies the sentinel node in more than 90 percent of women. Elsewhere in this issue of the *Journal*, Krag et al. report similar results in a large multicenter trial.<sup>45</sup> The positive predictive value of a successful sentinel-node biopsy approaches 100 percent, whereas its negative predictive value exceeds 95 percent.<sup>44,45</sup> Many patients with clinically negative axillary lymph nodes could be spared an axillary dissection if the sentinel node was found to be negative.

An alternative approach is to analyze the primary tumor for nuclear or histologic grade, kinetics of cell growth and division, hormone-receptor expression, markers of invasive or metastatic capability, or blood-vessel content. A combination of these prognostic markers might provide an acceptable substitute for the information derived from axillary lymph-node examination. Until these newer techniques are vali-



**Figure 1.** Individual and Pooled Odds Ratios for Survival at 10 Years in Women with Breast Cancer Treated by Breast-Conserving Therapy as Compared with Mastectomy.

Breast-conserving therapy consisted of breast-conserving surgery plus radiation. The horizontal bars indicate 95 percent confidence intervals. For the pooled data, the odds ratio is 0.9 (95 percent confidence interval, 0.8 to 1.0). IGR denotes Institut Gustave-Roussy, NSABP National Surgical Adjuvant Breast and Bowel Project, NCI National Cancer Institute, and EORTC European Organization for Research and Treatment of Cancer. Adapted from Fisher,<sup>39</sup> with the permission of the publisher.

dated, axillary dissection remains the standard of care for all women with invasive breast cancer or large non-invasive tumors (>2.5 cm).

**Radiotherapy**

Radiotherapy is an integral part of breast-conserving treatment.<sup>34,38</sup> A recent randomized trial showed that administering chemotherapy before radiotherapy resulted in higher survival rates when both chemotherapy and radiotherapy were given postoperatively.<sup>46</sup>

Postmastectomy radiotherapy reduces the incidence of local and regional recurrences by 50 to 75 percent, but in most randomized trials, and according to a meta-analysis, this reduction was not accompanied by increased survival.<sup>47-50</sup> For that reason and because of its potential for long-term adverse effects, radiotherapy after mastectomy is indicated only for women at high risk for local or regional recurrence (patients with large tumors invading the skin of the breast or the chest wall or those with many positive axillary lymph nodes). However, in two recent, long-term randomized studies of high-risk premenopausal women with breast cancer treated with modern radiotherapy techniques and chemotherapy or with chemotherapy alone, there were fewer local and regional recurrences and overall survival was significantly better among the women treated with radiotherapy and chemotherapy (Table 2).<sup>51,52</sup> These results have renewed interest in postmastectomy radiotherapy.

**TABLE 2.** TEN-YEAR CANCER-FREE SURVIVAL AND OVERALL SURVIVAL AMONG WOMEN TREATED WITH CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY AFTER MASTECTOMY.

| STUDY AND OUTCOME                                    | NO. OF SUBJECTS | PERCENT SURVIVING |                               | P VALUE |
|--|-----------------|-------------------|-------------------------------|---------|
|  |                 | CHEMOTHERAPY      | CHEMOTHERAPY AND RADIOTHERAPY |         |
| British Columbia <sup>51</sup>                       | 318             |                   |                               |         |
| Cancer-free survival                                 |                 | 41                | 56                            | 0.007   |
| Overall survival                                     |                 | 54                | 64                            | 0.07    |
| Danish Breast Cancer Cooperative Group <sup>52</sup> | 1708            |                   |                               |         |
| Cancer-free survival                                 |                 | 34                | 48                            | <0.001  |
| Overall survival                                     |                 | 45                | 54                            | <0.001  |

**Systemic Hormone Therapy or Chemotherapy**

The optimal treatment for women with primary breast cancer involves multiple methods and includes systemic therapy with hormonal agents, combination chemotherapy, or both. Over the past 25 years, various aspects of systemic therapy have been studied in many randomized trials, and there have been four overviews of data from the available randomized trials.<sup>53-56</sup> Current knowledge is based on about 400 trials including more than 220,000 women. Hormonal therapy and chemotherapy added to local

treatment favorably alter the natural history of breast cancer. The reduction in the rates of recurrence and death persists beyond 15 years for all forms of systemic treatment. Most women with primary breast cancer have sufficient residual risk after regional therapy to benefit from systemic therapy, but for some the benefit is marginal. The indications for systemic adjuvant therapy are shown in Table 3.

For adjuvant therapy, combination chemotherapy is more effective than single-drug therapy, reducing the annual risk of death by about 20 percent.<sup>53</sup> Although the effects of combination chemotherapy are more marked in women younger than 60 years, especially those who are premenopausal when therapy is begun, its effectiveness has been clearly demonstrated up to the age of 69 years. Adjuvant tamoxifen therapy significantly reduces the risks of recurrence and death in women in all age groups. The benefit is greater when tamoxifen is administered for about five years, rather than one to three years, and when it is given to women with estrogen-receptor-positive tumors.<sup>54</sup> Recent analyses suggest that women with estrogen-receptor-negative tumors should not be treated with hormonal therapy. Treatment for more than five years is no more effective than treatment for five years.<sup>57</sup>

**Preoperative Chemotherapy**

Chemotherapy is usually administered after surgery in women with operable breast cancer. However, for women with large operable tumors, preoperative chemotherapy may have some advantages. Several reports<sup>53,58</sup> have indicated that close to 90 percent of primary operable tumors decrease in size by more than 50 percent after chemotherapy, thus making lumpectomy a possibility for many women who would

otherwise have required a mastectomy. In terms of survival, there is no apparent advantage to preoperative chemotherapy as compared with postoperative chemotherapy.

**Duration of Chemotherapy**

In several trials, combination treatment for less than three months was inferior to treatment for four to six months, whereas treatment with a single combination-chemotherapy regimen, such as cyclophosphamide, methotrexate, and fluorouracil (CMF), for longer than six months was no more effective than treatment for four to six months.<sup>53,55,59</sup> The combinations used most often are fluorouracil, doxorubicin, and cyclophosphamide (FAC); fluorouracil, epirubicin, and cyclophosphamide (FEC); doxorubicin and cyclophosphamide (AC); and CMF. These combinations are administered intermittently at intervals of three to four weeks. Six cycles of FAC or FEC (duration, 18 to 24 weeks), six cycles of CMF (duration, 18 to 24 weeks), or four cycles of AC (duration, 12 to 16 weeks) are considered standard therapy. A recent report of the preliminary results of a large randomized trial suggested that the addition of four cycles of paclitaxel (duration, 12 to 16 weeks) to four cycles of AC improved both disease-free survival and overall survival rates.<sup>60</sup> In premenopausal women, ovarian ablation has a substantial benefit, equivalent to that of combination chemotherapy or tamoxifen.<sup>53,56</sup> This benefit persists for 15 years after treatment.

**Combination Chemotherapy and Hormone Therapy**

The combination of tamoxifen (or ovarian ablation for premenopausal women) and chemotherapy is more effective than either alone.<sup>53,55,56,59</sup> Therefore,

**TABLE 3. INDICATIONS FOR ADJUVANT SYSTEMIC THERAPY AFTER SURGERY IN WOMEN WITH OPERABLE BREAST CANCER.**

| TYPE OF DISEASE  | ADJUVANT THERAPY INDICATED*             |
|--|---|
| Breast cancer without evidence of invasion   |   |
| Noninvasive breast cancer (ductal or lobular carcinoma in situ)  | None                                    |
| Breast cancer with evidence of invasion, but negative axillary lymph nodes   |   |
| Microinvasive breast cancer (<1 mm in largest diameter)  | None                                    |
| Invasive ductal or lobular carcinoma <1 cm in largest diameter   | None                                    |
| Invasive carcinoma <3 cm in largest diameter with favorable histologic findings (pure tubular, mucinous, or papillary) | None                                    |
| Invasive ductal or lobular carcinoma ≥1 cm in largest diameter   | Chemotherapy, hormonal therapy, or both |
| Invasive carcinoma ≥3 cm in largest diameter with favorable histologic findings (pure tubular, mucinous, or papillary) | Chemotherapy, hormonal therapy, or both |
| Invasive breast cancer with positive axillary lymph nodes  |   |
| All tumors, regardless of size or histologic findings  | Chemotherapy, hormonal therapy, or both |

\*Chemotherapy consists of fluorouracil, doxorubicin, and cyclophosphamide (FAC); doxorubicin and cyclophosphamide (AC); or cyclophosphamide, methotrexate, and fluorouracil (CMF). Hormonal therapy consists of tamoxifen or ovarian ablation (either surgical or chemical).

the combination of chemotherapy and tamoxifen is recommended, especially for women with a high risk of recurrent disease. There is substantial agreement about the choice of optimal adjuvant therapy once it has been determined that a woman might benefit from this intervention (Table 4).

**Dose-Intensive and High-Dose Chemotherapy Regimens**

In dose-intensive regimens, chemotherapy is administered in conventional doses but at shorter intervals; in high-dose regimens, chemotherapy is given in doses higher than conventional doses. Although preliminary results with these regimens are encouraging, there is no evidence from randomized trials that either type of regimen is more effective than standard-dose adjuvant chemotherapy or than chemotherapy and hormonal therapy combined. Ongoing randomized trials should help to determine the efficacy of high-dose regimens and new therapeutic agents as curative treatments in breast cancer.<sup>61,62</sup>

**Locally Advanced and Inflammatory Breast Cancer**

Stage III breast cancer includes tumors larger than 5 cm in the largest diameter, tumors of any size with direct invasion of the skin of the breast or the chest wall, and any tumors with fixed or matted axillary lymphadenopathy. Women with stage III or locally advanced breast cancer should be treated with preoperative chemotherapy or hormonal therapy, surgery, and radiotherapy.<sup>63,64</sup> In more than 65 percent of such women, the tumors shrink by more than 50

percent with preoperative chemotherapy. Most previously inoperable tumors become operable, and some become amenable to breast-conserving therapy.<sup>64</sup> Limited data suggest that adjuvant chemotherapy and hormonal therapy are indicated after preoperative chemotherapy and regional treatment.<sup>65</sup> Excellent local control can be achieved in 80 to 90 percent of women, and about 30 percent of women with stage IIIB tumors (tumors with direct invasion of the skin of the breast or the chest wall) or inflammatory breast cancer remain free of cancer after 10 years.<sup>63,66</sup>

**Metastatic Breast Cancer**

The clinical course of metastatic breast cancer is variable; this heterogeneity results in large variations in growth rate and responsiveness to systemic therapy. Chemotherapy, hormonal therapy, radiotherapy, and limited surgery are all used in the treatment of women with metastatic breast cancer,<sup>67</sup> although the overwhelming majority of these women will die of their disease.<sup>68</sup> Therefore, optimal palliation and prolongation of life are the main goals of treatment. It is important to use all available treatments to obtain maximal control of symptoms, prevent serious complications, and prolong life with minimal disruption of the woman's lifestyle and quality of life (Fig. 2).

**Diagnosis**

Frequent testing to identify recurrences and metastases in order to institute aggressive treatment has not altered the clinical course of women with meta-

**TABLE 4. SELECTION OF ADJUVANT SYSTEMIC THERAPY FOR WOMEN WITH OPERABLE PRIMARY BREAST CANCER AND INDICATIONS FOR ADJUVANT TREATMENT.**

| CHARACTERISTICS OF PATIENT AND TUMOR | LEVEL OF RISK            | ADJUVANT SYSTEMIC THERAPY* |
|--------------------------------------|--------------------------|----------------------------|
| AGE                                  | ESTROGEN-RECEPTOR STATUS |                            |
| <50 yr                               | Negative                 | Any                        |
|                                      | Positive                 | Low                        |
|                                      | Positive                 | Moderate or high           |
|                                      |                          | Unknown                    |
| ≥50 yr                               | Negative                 | Any                        |
|                                      | Positive                 | Low                        |
|                                      | Positive                 | Moderate or high           |
|                                      |                          | Unknown                    |

\*Chemotherapy consists of fluorouracil, doxorubicin, and cyclophosphamide (EAC); doxorubicin and cyclophosphamide (AC); or cyclophosphamide, methotrexate, and fluorouracil (CMF). Hormonal therapy consists of tamoxifen or ovarian ablation (either surgical or chemical).

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