Improving Outcomes in Early-Stage Breast Cancer

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1.0 Category 1 credit

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PROGRAM OVERVIEW

Program Title
The Criteria for Improving Outcomes in Early-Stage Breast Cancer: Guidelines, Individualized Treatment, and Enhanced Communication.

Statement of Need
Breast cancer is the most prevalent type of cancer among women in the United States. It is the second leading cause of cancer-related deaths in this population, despite the fact that the majority of women with newly diagnosed breast cancer have early-stage breast cancer (ESBC), which has a favorable prognosis. Nonetheless, specific practice patterns in the treatment of ESBC prevent optimal clinical outcome for some patients. Established national guidelines for the surgical and adjuvant treatment of ESBC are frequently not followed, with particular patient subpopulations disproportionately affected by these disparities in care. Furthermore, a plethora of evidence indicates not only that doctor-patient communication is crucial to patient satisfaction and outcomes, but also that this type of communication is often inadequate in meeting the needs of the patient. Finally, in recent years a new set of unmet needs has been acknowledged – that of the breast cancer survivor, specifically with respect to smoothing the transition to management by a primary care provider.

This monograph will present current guidelines with discussion focused on circumstances and reasons for nonadherence as well as proposed strategies for increasing the use of guideline-recommended care for these patients. Additionally, the importance of and strategies for improvement of doctor-patient communication, the needs of breast cancer survivors, and the value of staying up-to-date of current and emerging data in the field of ESBC will be explored.

Target Audience
This is a 1-hour activity accredited for oncologists, physician assistants, nurse practitioners, nurses, and pharmacists.

Learning Objectives
Upon completion of this activity, participants should be able to:

• Implement current evidence-based guidelines for breast-conserving surgery, lymph node dissection, radiation therapy, and radical mastectomy into your practice, specifically taking into consideration the preferred first-line course and need for individualized treatment of patients with ESBC
• Design and employ individualized surgical, adjuvant, and endocrine therapy regimens for patients with postmenopausal, hormone receptor-positive ESBC, and incorporate ongoing discussions with patients regarding the importance of compliance throughout the prescribed course of treatment
• Conduct an informed and interactive clinical consultation for each patient with ESBC, including discussion of multiple alternative treatment options, and provide opportunities for the patient to request prognosis information and second opinions
• Implement a checklist-based system for transferring case-specific data to primary care physicians and patients to improve long-term survivorship care of ESBC patients
• Summarize recent clinical findings of hormone therapy and chemotherapy regimens for ESBC, interpret how they may benefit patients with hormone-sensitive breast cancer, and select appropriate patients to enroll in active clinical trials for treatment of ESBC

Accreditation and Designation

Physicians
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Kentucky College of Medicine and The Center for Medical Knowledge. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The University of Kentucky College of Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentations is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.

Physicians Assistants
AAPA accepts AMA PRA Category 1 Credits™ from organizations accredited by the ACCME.

Nurse Practitioners
AANP accepts AMA PRA Category 1 Credits™ from organizations accredited by the ACCME.

Nurses
TCL Institute, LLC is a provider approved by the California Board of Registered Nursing, Provider Number 15225, for 1.2 contact hours. RNs outside of California must verify with their licensing agency for approval of this course.

Pharmacists
The University of Kentucky College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.
PROGRAM OVERVIEW (continued)

Pharmacists (continued)

This knowledge-based activity has been assigned ACPE #022-999-10-071-H04-P and will award up to 1.0 contact hour (0.1 CEU) of continuing pharmacy education credit in states that recognize ACPE providers.

Statements of credit will indicate hours and CEUs based on participation and will be issued online at the conclusion of the activity. Successful completion includes completing the activity, its accompanying evaluation and posttest (score 70% or higher) and requesting credit online at conclusion of the activity. The College complies with the Accreditation Standards for Continuing Pharmacy Education.

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Accordingly:

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Dr. Terry Mamounas reported that he is a consultant to and speaker for sanofi-aventis U.S. LLC and Genomic Health, Inc. He also reported that he is a consultant to Genentech, Inc.; Novartis Corporation; and Bayer Corporation.

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To resolve identified conflicts of interest, the educational content was fully peer-reviewed by a physician who has nothing to disclose. The resulting certified activity was found to provide educational content that is current, evidence-based, and commercially balanced.

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Physicians, Physician Assistants, Nurse Practitioners, and Pharmacists

The method of participation for physicians, physician assistants, nurse practitioners, and pharmacist is as follows:

1. Complete the activity in its entirety
2. After the activity, go to www.CECentral.com/getcredit
3. Enter activity code XENN9095
4. Select the type of credit you wish to claim
5. Log in or register for a free account
6. Complete the evaluation
7. Get credit. A printable certificate will be available.

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Nurses only should log onto http://www.TotalMedEd.com/links/9044GMonograph/index.html and complete the online evaluation to receive credit. A printable certificate will be available upon completion of the activity evaluation.

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Support Statement

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Improving Outcomes in Early-Stage Breast Cancer

ABSTRACT

Early-stage breast cancer is a prevalent malignancy that continues to cause a significant number of cancer-related deaths each year. Current evidence points to suboptimal care in patients with early-stage breast cancer, especially with regard to physician use of guideline-recommended care. Such appropriate treatment regimens as breast-conserving therapy and adjuvant therapy (including radiation therapy, chemotherapy, and hormonal therapy) are underutilized in this patient population. Critical steps toward optimizing the appropriate treatment of early-stage breast cancer and providing the most significant benefits for patients include increasing awareness of potential barriers and developing strategies to overcome them. Improved communication, increased proactive behavior in terms of emerging data, and promotion of clinical trial participation may additionally improve outcomes in this patient population. This review incorporates pertinent oncology literature in a comprehensive overview of early-stage breast cancer treatment, including a review of existing guidelines, race and age disparities, and communication strategies for oncologists. The focus is on appropriate, evidence-based treatment of this patient population.

It is estimated that more than 207,000 women will be diagnosed with breast cancer in 2010,[1] the majority of these women will have early-stage disease.[2] Breast cancer survival has increased dramatically since 1975, from a 5-year survival rate of 75.5% for all patients combined to a rate of 90.6% in 2002.[3] This improvement in survival is also manifested in decreased breast cancer mortality rates across all age groups, although the largest magnitude of benefit appears in patients over 70 years old.[4] While survival is highly favorable overall for patients with early-stage disease, it decreases dramatically within this category by stage, from a 5-year relative survival of 100% for stage I disease to only 67% for stage IIIA disease.[5]

Although survival is the most crucial outcome for patients with early-stage breast cancer (ESBC), because many patients have excellent long-term outcomes, minimizing morbidity from treatment is also highly important. Each treatment modality used in the management of ESBC has numerous associated morbidities: some unique to a particular modality and some overlapping with other modalities. For instance, radiation therapy can increase the risk of cardiac dysfunction, lung dysfunction, and secondary cancers.[6] Chemotherapy and other systemic therapies may put patients at risk for both permanent side effects (infertility, cardiac dysfunction) and transient side effects (cognitive impairment, nausea, fatigue, hair loss).[7-10] Hormonal therapy can lead to bone loss, hot flashes, and arthralgia.[11] Even surgical procedures can have long-term implications for a patient’s health, as in the case of lymphedema and decreased arm function in patients who have undergone axillary lymph node dissection (ALND).[12] Thus, treatment of ESBC should be based on a careful risk/benefit analysis. This monograph will explore ways to improve the outcomes of women with ESBC.

Treatment for ESBC: Guidelines and Adherence

Need for Any Type of Adjuvant Therapy

According to breast cancer treatment guidelines developed by the National Comprehensive Cancer Network (NCCN), adjuvant therapy—which may include chemotherapy, hormonal therapy, targeted therapy, and/or radiation therapy—should be used for women over 70 years old who have lymph node involvement or
tumors greater than 1 cm in diameter. [13] However, compliance with these guidelines is poor; a recent study of 354 patients from 6 surgical oncology practices in the northeastern United States with stage 0, stage I, or stage II/III/node-negative disease reported that 40% did not receive guideline-recommended care, which included surgery, radiation therapy, and hormonal therapy. [14] While this lack of compliance can represent either under- or overutilization of therapy, evidence suggests that adjuvant therapy is more often underutilized. Investigators from Mount Sinai School of Medicine examined the treatment of 723 women with ESBC treated surgically at four Mount Sinai hospitals and found that between 18% and 33% of those patients who could have benefited from adjuvant therapy did not receive it (the omitted therapies included radiation therapy after breast-conserving surgery [BCS], adjuvant chemotherapy, and hormonal therapy). [15]

In a study of 258 women with ESBC who underwent surgery but did not receive guideline-recommended adjuvant therapy (radiation therapy, chemotherapy, or hormonal therapy, where appropriate), the same group of investigators surveyed these patients regarding their care, knowledge, medical mistrust, and physician communication in an attempt to define reasons for this underutilization of care. [16] They reported that untreated women, compared to those who received adjuvant therapy, were less likely to know that adjuvant therapy improved survival. Moreover, they had greater mistrust of the medical system and less self-efficacy.

While this study identified some potential patient-centered explanations for underutilization of adjuvant therapy, another study conducted by Bickell and colleagues focused on the surgeon’s perspective. This study surveyed breast cancer surgeons who treated 119 women who did not receive guideline-recommended adjuvant therapy. [17] Investigators reported a nearly equal distribution among the top three reasons for underutilization: (1) the perceived risks, as judged by the surgeon, exceeded the expected benefits, (2) the patient refused treatment despite surgeon recommendation, and (3) the patient did not receive surgeon-recommended care for an unknown reason (termed system failures). The authors provided evidence that these system failures were likely often due to suboptimal interactions between a patient’s surgeon and her medical oncologist, as when patients were referred to an oncology clinic rather than a specific oncologist’s office.

Breast-Conserving Therapy (BCS With Radiation Therapy)

In 1990, the National Institutes of Health (NIH) released guidelines stating that breast-conserving therapy (BCT) is appropriate treatment for the majority of women with stage I and II breast cancer, and that it is preferable because it provides survival that is equivalent to total mastectomy and axillary dissection while preserving the breast. [18] Similarly, the 2010 NCCN guidelines state that BCT consisting of lumpectomy, ALND, and whole-breast irradiation is equivalent to mastectomy with axillary dissection as primary breast treatment for the majority of women with stage I and II breast cancers. [13] This statement is based on numerous studies demonstrating that BCT produces equivalent survival to that of mastectomy (Table 1). BCT has increased over time, but stage II patients lag behind stage I patients in utilization rates. [19]

The National Cancer Institute (NCI) recently reported data suggesting that BCS is underutilized, with 35% of patients with stage I or II disease receiving mastectomy. [25] Predictors for underutilization of BCS that have been identified by a number of investigators are listed in Table 2. [26-30] These predictors vary, with some being associated with patient/tumor characteristics (lower socioeconomic status, larger tumor size), and others associated with characteristics of the surgeon (male gender, surgical training outside the United States), and others associated with a variety of factors (lower BCS reimbursement, residence outside a metropolitan area).

Despite research showing that radiation therapy following BCS reduces local recurrence rates and increases survival, [31] the NCI has reported that radiation therapy is omitted from BCT in one-third of women receiving BCS. [25] Predictors for omission of radiation therapy include older age, tumor size greater than 2 cm, negative nodes, treatment by surgical oncologist, and residence in the western United States. [26,29,32] It should be mentioned that omission of radiation therapy may not be considered underutilization for patients older than 70 with hormone receptor (HR)-positive disease who are being treated with hormonal therapy; recent data have demonstrated that outcomes in this patient population did not improve with the addition of radiation therapy to BCS. [33]

### Table 1

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Length of OS</th>
<th>OS Results: BCT vs Mastectomy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Dongen, 2000[21]</td>
<td>868</td>
<td>10 yr</td>
<td>65% vs 66%</td>
<td>.11</td>
</tr>
<tr>
<td>Fisher, 2002[22]</td>
<td>1851</td>
<td>20 yr</td>
<td>RR: 0.97</td>
<td>.74</td>
</tr>
<tr>
<td>Veronesi, 2002[23]</td>
<td>701</td>
<td>20 yr</td>
<td>41.7% vs 41.2%</td>
<td>1.0</td>
</tr>
<tr>
<td>Poggi, 2003[24]</td>
<td>237</td>
<td>18.4 yr</td>
<td>54% vs 58%</td>
<td>.67</td>
</tr>
</tbody>
</table>

OS = overall survival; RR = relative risk.
Lymph Node Dissection

Two different national guidelines—from the NCCN and the American Society of Clinical Oncology (ASCO)—support the use of sentinel lymph node biopsy (SLNB) for patients with clinically node-negative breast cancer.[13,34] A small randomized study of patients with negative sentinel lymph nodes provided early support for this approach; the study found that SLNB was associated with equivalent breast cancer–related events ($P = .52$) and a trend toward increased survival ($P = .15$) compared with ALND.[35] Sentinel lymph node biopsy has several advantages over ALND, including decreases in lymphedema, sensory loss, drain usage, length of hospital stay, and time to resumption of normal daily activities; and increases in patient-recorded quality-of-life (QOL) and arm function scores.[12] The NCCN guidelines also support SLNB for clinically positive lymph nodes if they are found to be negative by fine needle aspiration or core biopsy prior to surgery.[13] Acceptance of SLNB is high, and SLNB alone for patients with negative sentinel nodes is currently the accepted standard of care.[12]

Recent data from two independent studies presented at the 2010 ASCO annual meeting confirmed that, compared to SLNB, ALND did not improve outcome in patients with clinically node-negative disease, regardless of whether the disease was sentinel node–negative or sentinel node–positive.[36,37] However, results from the study examining node-negative disease must be interpreted with caution, as it did not reach its accrual goal and was thus underpowered.

Chemotherapy

The 2000 NIH consensus statement recommends chemotherapy for women with node-positive tumors or with node-negative tumors larger than 1 cm, regardless of HR status.[38] Largely similar are the 2010 NCCN breast cancer guidelines, which support the use of adjuvant chemotherapy for women with lymph node–positive disease or with lymph node–negative, HR-negative tumors larger than 1 cm; the guidelines also state that chemotherapy should be considered for women with lymph node–negative, HR-negative tumors between 0.6 and 1.0 cm in size.[13] Each of the NCCN’s seven preferred combination adjuvant chemotherapy regimens contain an anthracycline (doxorubicin), a taxane (docetaxel), or both.[13] The Early Breast Cancer Trialists’ Collaborative Group has performed several meta-analyses showing that combination chemotherapy reduces the risk of death from breast cancer in women with ESBC, and three of their publications have reported that this survival advantage is present largely regardless of HR status or nodal status.[39–41]

Despite the overwhelming evidence that adjuvant chemotherapy has a survival advantage in patients with ESBC, some studies have shown that it is underutilized in ESBC populations, regardless of these disease characteristics: node-negative, node-positive, HR-negative, HR-positive.[14,42,43] While it is true that adjuvant chemotherapy improves the overall survival of patients with ESBC, not all patients in this population benefit from it. Adjuvant chemotherapy can come at a high cost with respect to financial resources and acute and chronic side effects. Therefore, it is desirable to limit adjuvant chemotherapy to only those patients most likely to derive benefit. Within the past decade, genomic profiling tools designed to help identify such patients have become available. The most widely used of these tools in the United States is the 21-gene recurrence score assay, which has been developed for patients with HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-negative disease.[44] Using the reverse-transcriptase polymerase chain reaction profiles of 16 tumor-associated genes and 5 housekeeping genes, a recurrence score can be calculated that classifies patients into 3 categories: low, intermediate,
and high risk for recurrence when treated with tamoxifen. Patients with a low recurrence score are unlikely to benefit from chemotherapy and, thus, may reasonably avoid an expensive, potentially toxic treatment.[45] It is currently unclear whether patients with an intermediate recurrence score derive substantial benefit from chemotherapy.[45] but TAI-LORx (Trial Assessing Individualized Options for Treatment for Breast Cancer), an international randomized trial, seeks to address this issue.[46] This trial will complete accrual later in 2010.

Hormonal Therapy
Tamoxifen was the first hormonal agent to demonstrate a survival advantage in the adjuvant setting.[47] More recently, the third-generation aromatase inhibitors (AIs) were investigated as potential therapies to improve outcomes in postmenopausal women with ESBC.[48-55] As a class, the AIs have a safety profile that is distinct from that of tamoxifen. Whereas patients taking tamoxifen have an increased risk of endometrial cancer and thromboembolic disease, patients taking AIs have an increased risk of arthralgia, myalgia, and bone loss. [56] The life-threatening nature of the increased risk of tamoxifen-specific toxicities creates a safety profile for tamoxifen that is less favorable than that of the AIs.

A number of randomized clinical trials have reported positive results with the three commercially available AIs. Three different approaches to hormonal therapy have been examined: (1) up-front therapy, in which an AI is compared to tamoxifen, (2) sequential therapy, in which the AI is given 2 to 3 years after completion of tamoxifen treatment, and (3) extended adjuvant therapy, in which an AI is given 5 years after completion of tamoxifen treatment.

The first clinical trial to report favorable results with up-front therapy was the ATAC (Arimidex, Tamoxifen, Alone and in Combination) trial, which demonstrated that anastrozole (Arimidex) produced superior disease-free survival (DFS) compared to tamoxifen.[48] The TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial was an international study of nearly 10,000 patients that examined exemestane (Aromasin) as up-front therapy vs sequential therapy of tamoxifen followed by exemestane.[49] Jones and colleagues reported that, after a median follow-up of 5 years, both regimens produced similar DFS, overall survival (OS), and recurrence rates, showing that exemestane used as up-front or sequential therapy provides similar results to tamoxifen in women with ESBC.

The third up-front therapy trial, BIG (Breast International Group) 1-98, was designed to compare 5-year treatment with letrozole (Femara) to tamoxifen.[50] The initial design was one of up-front therapy, with patients to receive either letrozole or tamoxifen. But because positive results were being published with sequential therapy, the trial was amended to include two additional arms: 2 years of tamoxifen followed by 3 years of letrozole and 2 years of letrozole followed by 3 years of tamoxifen.

Up-front therapy results showed that patients receiving letrozole showed a significant 19% improvement in DFS (hazard ratio, 0.81; \( P = 0.003 \)) and a reduced risk of distant recurrence (hazard ratio, 0.73; \( P = .001 \)) compared to those receiving tamoxifen. When examining the sequential therapy arms of the BIG 1-98 trial, both had similar DFS rates after 5 years, with 87.6% for letrozole followed by tamoxifen and 86.2% for tamoxifen followed by letrozole, and neither was superior to letrozole monotherapy.[51] Switching from letrozole to tamoxifen after 2 to 3 years had no impact on patient outcomes, with the letrozole monotherapy arm and the letrozole → tamoxifen arm both having similar DFS and OS rates at 5 years.[51] This indicates that patients who are intolerant of letrozole or who have developed bone loss in the first 2 to 3 years should be able to switch to tamoxifen without compromising outcome.

The IES (Intergroup Exemestane Study) trial, which took a sequential approach to therapy by randomly assigning patients to receive either 5 years of tamoxifen or to 2 to 3 years of tamoxifen followed by 2 to 3 years of exemestane, showed that patients who switched from tamoxifen to

<table>
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<tr>
<th>Table 3</th>
<th>Barriers to Adherence to Oral Hormonal Therapies—and Strategies to Overcome These</th>
</tr>
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<tbody>
<tr>
<td>Barriers to Adherence</td>
<td>Strategies to Overcome Barriers</td>
</tr>
<tr>
<td>Lack of tangible benefit</td>
<td>Discuss studies showing the benefit of adjuvant endocrine therapy</td>
</tr>
<tr>
<td>Lack of understanding of the importance of adherence</td>
<td></td>
</tr>
<tr>
<td>Length of treatment</td>
<td></td>
</tr>
<tr>
<td>Side effects of medication</td>
<td>Review potential side effects and develop management strategies, as needed</td>
</tr>
<tr>
<td>Busy schedule (not enough time to refill prescriptions)</td>
<td>Encourage mail-order prescription refills</td>
</tr>
<tr>
<td>Cost</td>
<td>Discuss strategies to decrease costs and save time (mail-order refills, discount drug programs)</td>
</tr>
<tr>
<td>Patient dissatisfaction with treating physician</td>
<td>Augment patient-provider communication by having the nurse solicit questions that may be intimidating or embarrassing</td>
</tr>
<tr>
<td>General barriers</td>
<td>Identify potential barriers; provide written information about the therapy; provide patient with professional contact information; schedule regular follow-up; provide a list of relevant organizations and support groups; explore specific needs/characteristics of the patient</td>
</tr>
</tbody>
</table>

Data from Miaskowski et al.[62] Moore.[63] and Kirk and Hudis.[64]
exemestane after 2 to 3 years had improved DFS compared with those who received 5 years of tamoxifen. [52] The next two sequential therapy trials—ARNO (Arimidex-Nolvadex) 95 and The Austrian Breast and Colorectal Cancer Study Group Trial 8—were similar to the IES trial in design but examined the use of anastrozole instead of exemestane. [53] Because they were nearly identical in design and inclusion criteria, the two trials were analyzed together. Results showed a significant improvement in event-free survival with anastrozole (hazard ratio, 0.60; \( P = 0.009 \)).

MA.17, an extended therapy trial, provided evidence that DFS was prolonged when patients received 5 years of letrozole after 5 years of tamoxifen. [54] Mamounas and colleagues conducted the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial to similarly test exemestane as extended adjuvant therapy. [55] In this trial, postmenopausal breast cancer patients who were disease-free after 5 years of tamoxifen were randomly assigned to receive either 5 years of exemestane (25 mg daily) or 5 years of placebo. Because of the positive results from the MA.17 trial, the NSABP trial was terminated and unblinded after approximately half of the patients had been accrued. Despite this reduction in power, results showed a borderline significant improvement in 4-year DFS in patients receiving exemestane (91% vs 89%; relative risk [RR], 0.68; \( P = 0.07 \)) as well as a significant improvement in 4-year relapse-free survival (96% vs 94%; RR, 0.44; \( P = 0.004 \)).

The use of AIs rather than tamoxifen is supported primarily by their more favorable safety profile and their ability to reduce the risk of recurrence, rather than by an ability to improve OS. Moreover, this choice of hormonal therapy is only available to postmenopausal women; tamoxifen is the only option for premenopausal women because AIs do not sufficiently block ovarian production of estrogen.

As a result of the above studies of hormonal agents, the NCCN recommends that hormonal therapy should be considered for patients with estrogen receptor– and/or progesterone receptor–positive invasive breast cancers regardless of patient age, lymph node status, or plans for adjuvant chemotherapy. [13] Despite these broad guidelines, adjuvant hormonal therapy is underutilized in women with HR-positive ESBC, with approximately 30% of patients not receiving hormonal therapy, regardless of nodal status. [57]

Several studies have shown that adherence to hormonal therapy by women with ESBC is low. For instance, Chlebowski and Geller reported that 23% to 28% of women who were enrolled in adjuvant breast cancer clinical trials prematurely discontinued hormonal therapy (tamoxifen or AIs) after at least 4 years of follow-up. [58] Clarkson and colleagues reported a similar percentage (23%) of older patients prematurely discontinuing adjuvant hormonal therapy. [59] Finally, in a study of almost 1,500 patients with HER2-positive, stage I or greater disease [13], the US Food and Drug Administration (FDA) approved adjuvant use of trastuzumab in November 2006. [60] Physician adherence to HER2 testing is high, with a recent study reporting 98.1% adherence to HER2 testing.

### Trastuzumab Therapy

Four large randomized trials examining adjuvant trastuzumab (Herceptin) therapy nearly simultaneously demonstrated that the addition of trastuzumab to adjuvant chemotherapy produced a dramatic DFS and overall survival advantage in patients with HER2-positive ESBC. [65-67] Reduction in the risk of DFS events ranged from 36% to 52% and reduction in the risk of death with trastuzumab ranged from 33% to 41%. As a result, practice was quickly changed to include adjuvant trastuzumab for patients with HER2-positive, stage I or greater disease [13].

### Table 4

<table>
<thead>
<tr>
<th>Survivorship Issues Specific to Patients With Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for continuing medical evaluation</td>
</tr>
<tr>
<td>Local complications of therapy (eg, lymphedema, pain, numbness)</td>
</tr>
<tr>
<td>Late complications of chemotherapy (eg, secondary leukemia, cardiac impairment, osteoporosis)</td>
</tr>
<tr>
<td>Gynecologic and reproductive issues (eg, infertility, amenorrhea, increased risk of endometrial cancer)</td>
</tr>
<tr>
<td>Management of menopausal symptoms</td>
</tr>
<tr>
<td>Discussion of hormone-replacement therapy</td>
</tr>
<tr>
<td>Psychosocial issues (eg, anxiety, mood disorders, sexual dysfunction)</td>
</tr>
<tr>
<td>Changes in lifestyle (eg, weight gain, exercise)</td>
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</table>

Adapted from Burstein and Winer. [88]
adherence in 322 patients for whom HER2 testing was indicated (breast cancers that are stage 1 or higher). [69] In this study, trastuzumab use was appropriately administered in 51 of 52 patients, with 1 patient having no documentation of HER2 overexpression. However, of the 45 patients with stage 2 or higher HER2-positive breast cancer, 13% did not receive trastuzumab. The reasons for this underutilization of trastuzumab were not explored in this study. However, because trastuzumab increases the risk of cardiotoxicity,[70] cardiovascular morbidity is one valid reason to avoid trastuzumab, particularly in patients with increased cardiovascular risk.

In the pivotal adjuvant trastuzumab trials, the incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab arm was 4.1% in the NSABP B-31 trial and 2.9% in the North Central Cancer Treatment Group N9831 trial.[65] Examination of cardiac dysfunction reported in the N9831 trial revealed that older age, lower baseline left ventricular ejection fraction, and antihypertensive medications are risk factors for trastuzumab-associated cardiac dysfunction.[71] Despite the risk of cardiotoxicity, it is widely accepted that the benefits of trastuzumab outweigh the risks for most patients.

Disparities in the Care of Patient Subsets

In the above section, different areas of treatment nonadherence were discussed in the context of the general ESBC population. However, nonadherence is not evenly distributed across the US patient population; rather, certain subgroups receive less guideline-recommended care than other subgroups. The following discussion will focus on US treatment disparities with respect to race and age.

Racial Disparities

In the United States, the incidence of breast cancer in Caucasians exceeds that in African Americans and other ethnicities[2]; however, breast cancer mortality is higher in African Americans than in Caucasians (Figure 1).[2] Although a number of factors may contribute to this disparity in mortality, including differences in breast cancer screening, tumor biology, genetic predisposition, demographics, and comorbidities, substantial evidence exists that treatment differences across races account for at least some of the observed disparity.[72]

Several independent studies examined two large US databases (Surveillance, Epidemiology, and End Results [SEER] and National Cancer Database) to identify treatment differences between African American and Caucasian women.[73-75] While no disparity in the rate of BCS was observed,[73] African Americans were reported to be 24% less likely to receive radiation therapy following BCS and to have lower odds of receiving definitive locoregional therapy, adjuvant hormonal therapy, and adjuvant chemotherapy.[74,75]

Racial disparities in the treatment of ESBC are not only confined to the African American population. In a cross-sectional study of 677 women with ESBC treated in New York, Bickell and colleagues found that race played a statistically significant role in the underutilization of appropriate adjuvant therapy, with Caucasians having the least underuse (16%), followed by Hispanics (23%) and African Americans (34%).[43] Hispanics are more likely to be diagnosed at later stages than Caucasians, even after poverty level is accounted for. [76] Furthermore, Hispanic patients with ESBC had the lowest rates of definitive local therapy of all races in an analysis of SEER data from over 375,000 women.[77]

Sometimes, treatment disparities may affect QOL more than survival, as in the case of Asian American women and their mastectomy rate. Asian Americans have higher rates of mastectomy than other races. Important factors that contribute to this increased rate include fear, cultural beliefs, smaller breast size, and patient attitudes toward preserving the breast.[78] A study of 93 patients who underwent either BCT or mastectomy revealed a modest but significant improvement in QOL with BCT compared with mastectomy.[79]

Age Disparities

It is well established that older women with breast cancer are treated less aggressively and with less adherence to treatment guidelines than are younger women. For instance, SEER data showed that increasing age was significantly associated with decreasing BCS rates, with 48% of patients older than 50 years receiving BCS, but only 35% of patients older than 80 years receiving the same treatment.[24] Similarly, numerous studies have concluded that older age...
(aged ≥ 70-80 years) is a predictor of less frequent utilization of radiation therapy following BCS than is seen with younger patients.\[26,29,32\] SEER data also showed that older women (aged ≥ 80 years) were less likely to undergo lymph node dissection as part of their BCT than younger women.\[80\] Finally, elderly patients (aged ≥ 70 years) with nodal involvement or HR-negative tumors were less likely to receive adjuvant chemotherapy than younger controls.\[81\]

While it is clear that older patients with ESBC are treated differently than their younger cohorts, the question is whether this is appropriate. There is a paucity of national guidelines on the topic of treating older patients with breast cancer, primarily because so few elderly patients enroll in clinical trials, making conclusions about their responses to treatment challenging. For instance, the NCCN does not make specific recommendations regarding the use of BCS in elderly patients and suggests that radiation therapy is not always necessary for women aged 70 years or older.\[13\] Yood and colleagues, however, demonstrated that older women receiving BCT with radiation therapy had similar mortality rates to those receiving mastectomy, whereas those receiving BCS alone (without radiation therapy) were twice as likely to die as those receiving mastectomy.\[82\] However, the NCCN recommendation that radiation therapy may be omitted in women aged 70 years or older who have HR-positive, node-negative T1 tumors\[13\] is supported by recent data presented at ASCO 2010: these data showed that patients aged 70 years or older with HR-positive disease who were treated with BCS with tamoxifen had approximately the same survival whether or not radiation therapy was added.\[33\]

The NCCN guidelines also state that both ALND and SLNB are optional in elderly patients due to the absence of definitive data demonstrating superior survival with the use of these procedures;\[13\] however, recent data show that older patients (aged 55 years or older) with small tumors are not less likely to have positive sentinel lymph nodes than a younger cohort,\[83\] suggesting that older patients should not be treated differently with respect to lymph node assessment.

Finally, the NCCN guidelines decline to make definitive chemotherapy recommendations for patients older than 70 years due to insufficient data.\[13\] In fact, a meta-analysis conducted by the EBCTCG found that the efficacy of combination chemotherapy in patients with ESBC declines with age (Figure 2).\[41\]

Older patients with breast cancer have an increased likelihood of having more favorable biologic tumor characteristics than younger patients,\[84\] which can translate into older patients with ESBC being treated less aggressively. Similarly, comorbidities (eg, hypertension, heart-related conditions, arthritis, and gastrointestinal problems) increase with age.\[85\] making it more challenging to provide adjuvant therapy to this patient population. In fact, comorbidities, including heart failure and diabetes, are not only associated with the underuse of adjuvant therapy;\[38\] they also have a significant negative effect on survival.\[86,87\] However, it is not an accepted fact that older patients with ESBC derive less benefit from adjuvant therapy than younger patients, with the possible exception of combination chemotherapy. When comparing adjuvant combination chemotherapy to single-agent capecitabine (Xeloda) in women aged 65 years or older, Muss and colleagues determined that, although moderate-to-severe toxicities were elevated in the combination chemotherapy arm (64% vs 33%), the more intense chemotherapy produced superior outcomes.\[88\] Patients on capecitabine had an almost two-fold increase in the risk of death compared with the patients on combination chemotherapy (\(P = .02\)). Older patients are most often inappropriately undertreated, primarily because of bias on the part of one or more parties—physicians, patients, or family members. It is possible that less aggressive management of breast cancer in older patients is only infrequently the result of medical complications. Thus, older patients should be treated according to guidelines whenever possible, as long as such treatment does not exacerbate existing comorbidities and does not cause significant side effects.

### Doctor-Patient Communication

The importance of doctor-patient communication is often ignored in the literature and in practice, but it has an enormous impact on patient care. For instance, a retrospective study of nearly 10,000 elderly women with breast cancer showed that consulting with a medical oncologist prior to surgery increased the likelihood of receiving guidelines-recommended care.\[89\] Another study of patients with breast cancer, specifically node-negative, HR-positive disease, demonstrated that patients with more favorable ratings of provider communication were more likely to receive adjuvant chemotherapy.\[90\]

However, the challenges involved in establishing effective doctor-pa-
tient communication are substantial. Results of a survey of over 1,100 women with ESBC and their surgeons demonstrated that patients and their surgeons disagreed about whether both BCS and mastectomy were discussed as treatment options, with patients in one-third of the cases reporting that both options had not been discussed while their surgeons asserted that they had.[91] Another study illustrated the dissatisfaction sometimes experienced by patients: in this survey of over 600 patients with breast cancer, 30% rated their physicians 5 or less on a scale from 1 (poor) to 10 (good) with respect to the completeness of information they received about their disease and treatment.[92] Moreover, Keating and colleagues reported that 78% of over 2,000 patients surveyed had experienced at least one of the following problems with their physician, which caused them to consider changing physicians: (1) not giving understandable answers to questions, (2) not taking enough time to answer questions, and (3) not giving enough medical information.[93]

Although physicians are often not adequately trained in communication skills, several groups have studied strategies for improving doctor-patient communication. These include increasing affective, or emotional, participation with the patient, attending to both verbal and nonverbal patient cues, encouraging patients to ask questions, and (3) not giving enough medical information.[93]

Breast Cancer Survivorship

Cancer survivorship is a relatively new area of research and care that acknowledges that the needs of patients with cancer diagnoses do not stop after active treatment is terminated. According to the Institute of Medicine (IOM), cancer survivorship care is a distinct phase of care that has been neglected in such diverse areas as advocacy, education, clinical practice, and research. In the 2006 seminal report on survivorship, From Cancer Patient to Cancer Survivor: Lost in Transition, the IOM proposed four essential components of patient-centered survivorship care: (1) prevention of recurrent and new cancers and other late effects; (2) surveillance for cancer spread, recurrence, or second cancers, and assessment of medical and psychosocial late effects; (3) intervention for consequences of cancer and its treatment; and (4) coordination between specialists and primary care providers (PCPs) to ensure that all of the survivors’ health needs are met. Burstein and Winer have also identified a number of specific breast cancer survivorship issues (Table 4),[98] many of which can be categorized under one of the four IOM essential components of survivorship care mentioned above; however, novel areas of need identified by these authors include psychosocial issues (eg, anxiety, mood disorders, and sexual dysfunction) and changes in lifestyle (eg, weight gain and the need for increased exercise).

Central to providing comprehensive survivorship care are cancer treatment summaries and survivorship care plans.[99] Although preparing a concise summary of previous treatment may appear to be a trivial and uncomplicated matter, the frequent separation of the various breast cancer treatments in time, space, and health care systems makes the likelihood of mistakes and oversight high. Thus, such a summary should be prepared to facilitate communication among providers. Survivorship care plans are also created to facilitate
the coordination of care with other physicians (eg, internal medicine specialists, PCPs, gynecologists) who can provide successful ongoing care for breast cancer patients. These plans must address not only immediate posttreatment and long-term effects of cancer treatment, but also the ongoing psychosocial burden of a cancer diagnosis, and the potential for late sequelae of treatment. Survivorship care plans, which are a relatively new concept, have yet to be widely used in practice.

The need for improved survivorship care is great, as attested by patients and physicians alike. A 2007 survey of PCPs revealed that confidence in caring for cancer survivors is not high; only 49% of respondents were comfortable having responsibility for surveillance of breast cancer recurrence and even fewer (41%) were confident that they were following standard surveillance guidelines for breast cancer recurrence.[100] The same survey reported that 57% of PCPs rated the current transfer of care from oncologists as fair or poor. From the patients’ perspective, this problem may be even more pronounced. Of 300 postmenopausal breast cancer survivors surveyed, only 28% reported satisfactory communication between their oncologist and their PCP.[101] While most survivors (more than 70%) were positive regarding the general care, psychosocial support, and health promotion provided by their PCPs, fewer perceived their PCPs as knowledgeable about late effects of therapy (59%), cancer follow-up (50%), and treatment of symptoms related to cancer or cancer therapies (41%).

Focus groups of patients, oncologists, and PCPs have revealed specific concerns regarding breast cancer survivorship: breast cancer patients reported difficulties transitioning to survivorship, including psychosocial and communication issues; oncologists often had difficulty discharging patients due to close relationships; and PCPs were concerned about time and training needed to provide survivorship care and about communication problems with oncologists.[102]

Cancer survivorship care is particularly relevant to patients with ESBC because the vast majority of them will spend many years as cancer survivors as a result of their favorable prognoses. In addition, they receive a wide range of different therapies, including surgical resection/reconstruction, hormonal therapy, chemotherapy, and radiation therapy, so they may be dealing with a multitude of chronic or late effects of therapy. Thus, this population of patients stands to derive great benefit from improvements in survivorship care.

**Ongoing Clinical Trials and Emerging Data**

Staying abreast of emerging data and ongoing clinical trials is crucial to providing optimal care to patients with ESBC. Practice-changing results are frequently unveiled at annual oncology conferences, such as those of ASCO, the European Society of Medical Oncology, and the San Antonio Breast Cancer Symposium. Even physicians who cannot attend these conferences can learn what was presented by attending seminars that report conference highlights, perusing conference websites, or taking special online CME courses.

Currently, over 40 phase III clinical trials in ESBC are ongoing.[103] Awareness of these trials is important not only in order to anticipate what clinical results are emerging, but also to provide patients the opportunity to participate in these clinical trials. See Table 5 for current phase III trials that are recruiting patients with ESBC.

**Conclusion**

Breast cancer is the most prevalent malignancy among women in the United States.[1] Although most women are diagnosed with early-stage disease, which has a favorable prognosis, breast cancer remains highly lethal, behind only lung cancer in the number of cancer-related deaths it causes each year.[1] Multiple lines of evidence clearly demonstrate that patients with ESBC often do not receive optimal care. One of the most obvious problems is lack of physician adherence to guideline recommendations, with respect to BCT, hormonal therapy, and chemotherapy. Moreover, particular subpopulations of patients are disproportionately affected by these disparities in care. Other areas of physician behavior that can create barriers to appropriate patient management include unsatisfactory doctor-patient communication, a lack of proactive behavior regarding emerging data, including the promotion of clinical trial participation, and inadequate care of patients after they have reached the survivorship stage, which can be decades-long for many patients with ESBC. Finally, because these patients often receive oral agents (eg, tamoxifen, AIs) as part of their treatment, patient adherence is also an obstacle to optimal care. As these issues are brought to the forefront of physicians’ awareness and strategies are developed to minimize problems in each area, patients with ESBC will reap the benefits through improvements in clinical outcomes.

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