M. D. ANDERSON CANCER CARE SERIES

Series Editors

Aman U. Buzdar, MD **Ralph S. Freedman, MD, PhD**

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Series Editors: Aman U. Buzdar, MD
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Editors

The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Breast Cancer

2nd edition

Foreword by John Mendelsohn, MD

Springer

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Foreword

This second edition of *Breast Cancer* continues the tradition of the M. D. Anderson Cancer Care Series. The book is oriented towards the needs of clinicians who manage breast cancer at every stage of the disease. Chapters are written by experts with a strong knowledge of research findings who also are active in the clinic and understand the practical needs of the patient and her physician.

Multidisciplinary care is a popular term today, but such care has been practiced at M. D. Anderson Cancer Center for decades. The physicians who assembled this book are experienced practitioners of multidisciplinary care. The authors of each chapter carry out their clinical activities at our Nellie B. Connally Breast Center, where they collaborate in providing complete patient care services at a single site.

The chapters start, logically, with prevention of breast cancer and personalized risk assessment, including genetics. These topics are followed by chapters on early detection, with emphasis on a variety of sophisticated imaging techniques and sampling of tissue. The various surgical options, including reconstruction, are thoroughly presented. Before medical oncology is introduced there are chapters dealing with the growing use of markers to predict prognosis and to select hormonal or chemotherapy treatments that are likely to succeed. The book concludes with issues related to survivorship, including re-entering social and job-related activities and dealing with questions related to sexuality and reproduction.

I recommend this book to anyone seeking to apply the science and art of medicine to patients with breast cancer and to women who wish to prevent the disease or have survived it. Readers will become up to date on recent discoveries in, for example, human cancer genetics, expression arrays, magnetic resonance imaging, and ultrasonography, as well as current approaches to managing the mental and social challenges with which breast cancer patients must deal. Clinicians who read this book will become more skillful health care providers, which is the aim of each of the volumes in the M. D. Anderson Cancer Care Series.

John Mendelsohn, MD
President
The University of Texas M. D. Anderson Cancer Center

Preface

This second edition of *Breast Cancer* marks a milestone in the M. D. Anderson Cancer Care Series, which now includes seven volumes. This second edition also serves as a reminder to us of the dramatic progress that is being made in molecular diagnostics and therapies for breast cancer.

A number of newer therapies have become available since the first edition of this book was published in 2001 and are discussed in this new edition. The preoperative systemic therapy approach long practiced at M. D. Anderson Cancer Center is now being adapted to allow rapid evaluation of newer therapies with small numbers of patients. To reflect advances in the pathologic characterization of breast cancer, the first edition chapter "Serum and Tissue Markers for Breast Cancer" has been replaced by two chapters: "Serum Tumor Markers and Circulating Tumor Cells" and "Histopathologic and Molecular Markers of Prognosis and Response to Therapy." All the original chapters have been revised to include important new information. For example, this edition includes new data on tamoxifen and raloxifene in breast cancer prevention, MRI screening in breast cancer, and the integration of bevacizumab and trastuzumab into current therapy—topics that highlight developments in prevention, screening, and therapeutics, respectively. A number of new tables and figures have been added as well.

The success of this series in providing a resource to clinicians in the community and elsewhere is a tribute to its many contributors and also to M. D. Anderson's Department of Scientific Publications, where the series has been carefully nurtured by Walter Pagel and many scientific editors.

Aman U. Buzdar, MD
Ralph S. Freedman, MD, PhD

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1 Multidisciplinary Care of Breast Cancer Patients: Overview and Implementation

Eric A. Strom, Aman U. Buzdar, and Kelly K. Hunt

Introduction

M. D. Anderson Cancer Center has long embraced a multidisciplinary approach to breast cancer care. At M. D. Anderson, multidisciplinary care is characterized by the consistent use of a defined "best" practice,

collaboration between treating physicians, and coordination of treatment delivery to optimize patient outcomes and convenience. These three elements of M. D. Anderson's multidisciplinary approach are exemplified in the Nellie B. Connally Breast Center, the Multidisciplinary Breast Planning Clinic, and the institutional breast cancer treatment guidelines.

Nellie B. Connally Breast Center

The Nellie B. Connally Breast Center arose from a collaborative medical model combined with a desire to make cancer treatment more convenient for patients. The Breast Center occupies approximately 30,000 sq. ft. on the fifth floor of the Lowry and Peggy Mays Clinic. This building was designed as a comprehensive outpatient facility for patients with breast, genitourinary, and gynecologic neoplasms. In addition to the multidisciplinary centers for each of these disease sites, the Mays Clinic includes comprehensive imaging and diagnostic services, together with outpatient surgery, interventional radiology, and chemotherapy facilities, making the Mays Clinic a convenient treatment facility for patients who do not require inpatient hospitalization. Also on the fifth floor of the Mays Clinic is the Julie and Ben Rogers Breast Diagnostic Clinic, which provides complete breast diagnostic services, including digital and analog mammography, sonography of the breast and regional lymph nodes, breast magnetic resonance imaging, and stereotactic core needle biopsy and fine-needle aspiration biopsy capabilities. Also adjacent to the Breast Center are the Breast Wellness Clinic and the Beth Sanders Moore Undiagnosed Breast Clinic. The Breast Wellness Clinic is intended for long-term follow-up of patients who have previously been treated for carcinoma of the breast. The Undiagnosed Breast Clinic is for assessment of patients who have not had a previous diagnosis of breast cancer and have clinical or radiographic breast abnormalities. The Plastic Surgery Clinic is also housed on the fifth floor of the Mays Clinic and provides reconstructive options for cancer survivors.

The Breast Center is staffed by surgical oncologists, medical oncologists, and radiation oncologists; the Breast Diagnostic Clinic is staffed by radiologists and pathologists; and the Undiagnosed Breast Clinic is staffed by specialists in breast cancer clinical assessment, risk evaluation, and risk-reduction interventions. In addition to physicians, nurses, and midlevel providers, the Breast Center staff also includes genetic counselors, research nurses, referral specialists, social workers, pharmacists, business center staff, patient service coordinators, and volunteers. Physicians from the Department of Stem Cell Transplantation and Cellular Therapy who work in other areas of the M. D. Anderson complex are also included in discussions of treatment planning when appropriate. Between 2,500 and 3,000 established patient visits and over 300 new patient and consultation assessments occur in the Breast Center each month.

The close proximity of the various services involved in breast cancer care allows patients to have nearly all of their clinic visits in a single building and encourages collaboration between physicians. Informal and impromptu consultations between colleagues are common, thanks to the Breast Center physicians' close proximity and collegial relationships. These frequent discussions about a patient's course of treatment help to ensure that everyone on the treatment team is up to date and that all team members have the opportunity to contribute their expertise during the overall course of treatment.

This emphasis on each individual patient's treatment course also guides the center's day-to-day operations. Whenever possible, appointments with different specialists are scheduled on the same day, and all appropriate tests are ordered before a patient's initial visit so that each physician will have all of the information pertinent to the patient's case when he or she arrives. As one can imagine, coordinating such a large number of patients, clinicians, support personnel, diagnostic tests, and treatments requires extensive planning and a certain amount of flexibility. In the Nellie B. Connally Breast Center, administrators, clinicians, nurses, and support personnel meet twice a month to discuss the center's daily operations and to address problems and offer solutions. The ultimate goal is to develop and maintain a system that is consistent and efficient, allowing clinicians more time to devote to the treatment of their patients.

Many aspects of this model can be reproduced on a smaller scale. In some centers, for example, it may be feasible to conduct planning clinics that focus on one or two common disease sites—such as breast, lung, genitourinary, or gastrointestinal tumors—in addition to a general oncology clinic for less common cancer types. In centers where a lower patient volume allows for weekly or twice-weekly planning conferences for each patient, having a centralized location for the delivery of patient care is less critical. Most important is the commitment of the care team to work together, especially during the planning phase, for the benefit of the patient and his or her family.

Multidisciplinary Breast Planning Clinic

The treatment of patients with breast cancer within the Nellie B. Connally Breast Center is generally guided by the institutional breast cancer treatment guidelines (see "Breast Cancer Treatment Guidelines" and the appendix to this chapter). However, within the context of these general guidelines, decisions must often be made that require consultation between clinicians from different specialties. Since the early 1960s, breast cancer specialists at M. D. Anderson have been holding a regularly scheduled clinic during which patients who require multidisciplinary care are examined and have their treatment plans discussed by a team of physicians.

The purpose of the Multidisciplinary Breast Planning Clinic is to design appropriate, individualized treatment plans for all patients who require

multidisciplinary care. The physicians in the clinic work together to determine the most appropriate treatments for each patient (combinations of surgery, radiation therapy, and systemic therapy) and the best sequence in which to deliver these treatments.

The Multidisciplinary Breast Planning Clinic is an integral part of M. D. Anderson's multidisciplinary approach to the care of breast cancer patients. The discussions that take place in the clinic not only ensure the highest quality of care for each individual patient but also strengthen cooperation and exchange of information among the various specialties involved in breast cancer care.

Types of Patients Examined

Patients are examined and discussed in the Multidisciplinary Breast Planning Clinic if their clinical presentation or disease stage at initial evaluation indicates that there may be a need for specialists from all disciplines to assess the patient before a specific course of treatment is initiated.

Patients with early-stage disease are seen in the planning clinic if there is difficulty in determining the appropriate type of surgery or the proper sequence of surgery and radiation therapy. (Patients with early-stage disease who will be treated with surgery alone generally do not require evaluation in the planning clinic.) Patients with stage II disease who are candidates for preoperative chemotherapy or endocrine therapy are seen in the planning clinic so that the feasibility of breast conservation therapy (surgery plus radiation therapy) can be determined.

Also routinely discussed in the planning clinic are patients with stage III disease and most patients with inflammatory breast carcinoma who are treated with curative intent. These patients are seen in the clinic before chemotherapy and again after 2–4 cycles of chemotherapy to determine the appropriate local therapy. In selected patients with locally advanced breast cancer whose tumors are decreased in size by initial chemotherapy, breast conservation therapy may be feasible.

Schedule and Participants

The Multidisciplinary Breast Planning Clinic is held two afternoons each week, and up to five or six patients may be examined and discussed at each session. Patients are scheduled several days in advance so that all diagnostic evaluations can be completed before the clinic session.

Each planning clinic session includes at least one breast cancer specialist from each of the following disciplines: surgical oncology, radiation oncology, medical oncology, and diagnostic imaging. While pathologists do not routinely attend, they are requested to participate in cases in which a major pathology question is anticipated. In addition, M. D. Anderson breast pathologists review all outside pathology slides prior to a patient's initial appointment at M. D. Anderson. This pathology report is essential to good

treatment planning. Faculty attend the planning clinic on a rotating basis, and the rotation is set in advance to ensure representation from all specialties that may participate in treating the particular patients being discussed.

The patient's primary physician attends, and any physician assuming the care of the patient at any time during treatment is also welcome to attend. In addition, the multidisciplinary planning clinic is open to fellows and trainees participating in rotations on the breast services and to visiting physicians.

Clinic Procedures

At the beginning of the planning clinic, the multidisciplinary team convenes in the conference room, and the first patient is presented to the group by the patient's primary physician. The physician gives a synopsis of the history and treatments. The current problem is defined, and the patient's radiologic studies are reviewed. The multidisciplinary team then goes to the examination room, where the patient is examined by a surgical oncologist, a medical oncologist, and a radiation oncologist. Each person is introduced to the patient and his or her family, and it is explained to them that the team is convened primarily to advise the attending physician. This avoids premature discussion with the patient and family before a complete recommendation is formulated. The diagnostic radiologist may also examine the patient to determine if any additional imaging studies may be helpful. After the examinations are complete, the members of the multidisciplinary team return to the conference room, where they deliberate about treatment approaches and formulate a final treatment recommendation. The patient waits in the clinic area during these deliberations. The patient's spouse and other family members or friends are welcome to accompany the patient and to be present during discussions with the primary physician.

Once the team reaches a decision, the primary physician dictates the team's recommendation in the patient's medical record so that the recommendation will be available to all members of the multidisciplinary team who encounter the patient during treatment and follow-up. The primary physician then goes to where the patient is waiting and relays the recommendation of the multidisciplinary team. Finally, the primary physician discusses the recommendation of the planning clinic with any other physicians involved in the patient's care who may not have been able to participate in the multidisciplinary discussion.

Breast Cancer Treatment Guidelines

For the purposes of discussing treatment, it is convenient to divide breast tumors into several broad categories as well as assign the tumor to a specific TNM stage group (Table 1–1). The categories include the nonmetastasizing in situ lesions (ductal carcinoma in situ [DCIS] and lobular carcinoma

Table 1–1. Staging System for Breast Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor (Note: Paget's disease associated with a tumor is classified according to the size of the tumor.)
T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional Lymph Nodes — Clinical (N)	
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

(continued)

Table 1–1. continued

N3a	Metastasis in ipsilateral infraclavicular lymph nodes(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Regional Lymph Nodes — Pathologic (pN)[a]

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC) (Note: ITC are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical [IHC] or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction.)
pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

[b]RT-PCR: reverse transcriptase–polymerase chain reaction.

pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

(continued)

Table 1–1. continued

pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

**Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1–2	M0
Stage IIIB	T4	N0–2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

*T1 includes T1mic.

in situ [LCIS]); early-stage invasive cancer (stage I and some stage II cancers); operable intermediate-stage disease (stage II and most stage IIIA cancers); inoperable locally advanced disease (stage IIIB and IIIC cancers, inflammatory breast cancers, some stage IIIA cancers, and the occasional stage IV cancer with oligometastatic involvement); and metastatic carcinoma (stage IV). In addition, there are uncommon clinical presentations that do not fit conveniently into this classification system. These include local-regionally recurrent disease and axillary involvement from unknown primary adenocarcinomas.

The breast cancer treatment guidelines in the appendix to this chapter were developed collaboratively and represent the current favored approach to various breast cancer scenarios at M. D. Anderson. The approach was developed by combining the best current practices with practices suggested by the outcomes of clinical trials at M. D. Anderson and was informed by compelling scientific evidence from other institutions. The most recent version of the breast cancer guidelines can be found at http://www.mdanderson.org/Cancer_Pro/CS_Resources/; the guidelines are typically updated every other year. The breast cancer multidisciplinary group is committed to ongoing collaborative research and makes a point of designing clinical trials for each major category of disease. Ideally, these trials permit the most rapid deployment of promising basic science research into the clinical setting. Whenever possible, patients are encouraged to participate in these clinical trials. A complete listing of clinical trials available at M. D. Anderson can be found at http://www.clinicaltrials.org.

In Situ Lesions

For in situ (noninvasive) lesions—LCIS and DCIS—careful pathology review is critical to the success of the decision-making processes (see appendix, panel 1). For example, it is important to distinguish accurately between LCIS and atypical lobular hyperplasia because the type of disease affects a patient's subsequent risk of developing an invasive carcinoma. Similarly, it is important to distinguish accurately between well-differentiated DCIS and atypical ductal hyperplasia, although there is not universal agreement about the dividing line between these entities. Physicians must clearly understand the pathologic criteria for these distinctions before attempting to apply these treatment guidelines. In general, the goal of treatment is to prevent the occurrence of invasive disease while minimizing the side effects of therapy.

Lobular Carcinoma In Situ

LCIS is not considered to be a precursor lesion, per se, for invasive cancer. Instead, it represents a histologic finding that correlates with an increased risk for the development of an invasive breast cancer. Typically, LCIS has no clinical manifestations and has no pathognomonic mammographic

signs. Although individuals with LCIS are at increased risk for the development of invasive breast lesions, these cancers are more likely to be ductal than lobular, and the risk is the same in the index breast and the contralateral breast. Therefore, for most LCIS lesions—with the possible exception of pleomorphic LCIS, a DCIS-like entity—no specific treatment is indicated, even if the lesion is incompletely removed at biopsy. After adequate work-up, which should include bilateral diagnostic mammography and pathology review, appropriate risk-reduction strategies are discussed with the patient. Patients with a finding of LCIS on biopsy should be approached similarly to patients with a strong family history or other high-risk characteristics.

Ductal Carcinoma In Situ

Patients with large (larger than 4 cm) or multicentric DCIS as evidenced by mammography, physical examination, or biopsy generally require a total glandular mastectomy. Lymph node dissection or sentinel lymph node evaluation is not useful for most patients with DCIS. However, because the risk of occult invasion increases dramatically with the volume affected by in situ carcinoma, it is not unreasonable to perform some type of nodal assessment in patients who have extensive DCIS. In the rare cases in which tumor metastases are identified in regional lymph nodes, it must be assumed that a small invasive breast cancer is present, and these patients are treated for presumed stage II invasive breast cancer. Patients who require mastectomy are routinely offered the option of breast reconstruction in the absence of anatomic or medical contraindications.

Patients with unifocal DCIS of intermediate size that can be excised with clear margins are generally offered the alternatives of breast conservation therapy or total mastectomy. These alternatives are presumed to be equally effective, although they have not been directly compared in large prospective trials. After providing adequate information about the probable risks and benefits, the physician largely leaves the choice of treatment up to the patient.

On the basis of results from a few small retrospective studies, patients with very small, unicentric, low-grade DCIS may be offered the additional option of excision alone without subsequent irradiation. Since the data about the appropriate management of low-risk DCIS are conflicting, individualized recommendations about observation versus irradiation will be necessary until the results of recently completed randomized trials become available. These and other ongoing prospective studies evaluating the role of local therapy and selective estrogen receptor modulators in the treatment of DCIS will be the primary motivators for future modifications to the current guidelines.

Tamoxifen has been demonstrated to reduce the short-term risk of local recurrence for patients with DCIS treated with excision and radiation therapy and has also demonstrated efficacy in preventing contralateral

breast cancer. The potential benefit of tamoxifen is weighed against the potential risk of tamoxifen for each individual patient.

In patients with DCIS treated with mastectomy, surveillance after treatment includes annual physical examination and diagnostic mammographic examination of the contralateral breast. In patients with DCIS treated with breast conservation therapy, surveillance includes semiannual physical examination and annual bilateral mammography.

Early-Stage Invasive Breast Cancer

The standard work-up for patients with early-stage invasive disease (see appendix, panel 2) includes complete breast imaging (typically bilateral diagnostic mammography and sonography of the breast and regional nodal basins), complete blood cell count with platelet count, liver function tests, and chest radiography. Any pathology specimens from outside institutions are reviewed by M. D. Anderson breast pathologists. The tumor size, pathologic subtype, differentiation, and nuclear grade are determined, along with the status of the surgical margins, the presence or absence of vascular lymphatic invasion, and the status of the regional nodes. The status of the estrogen and progesterone receptors and Her-2/*neu* amplification are also assessed. For most patients, no additional staging is indicated. A baseline bone scan is obtained in patients with stage I disease only when they have skeletal signs or symptoms. Similarly, baseline imaging of the liver is performed in patients with stage I disease only when they have abnormal findings on liver function tests.

Local Treatment

Initial local treatment is preferred for patients with tumors smaller than 1 cm and a clinically negative axilla. This is appropriate since the risk of systemic disease in most of these patients is not sufficient to warrant the use of cytotoxic chemotherapy. Patients with larger tumors are also referred for initial local treatment if they have significant comorbid illnesses and if histologic evaluation of the axilla will determine recommendations for systemic therapy. Since multiple prospective randomized trials have demonstrated that mastectomy is equivalent to breast conservation therapy in terms of survival benefit, most patients are offered both of these options for primary local therapy. This appropriately requires extensive patient education about the relative contraindications to breast conservation therapy, including prior irradiation of the breast (for example, for Hodgkin's disease), evidence of gross multicentricity or diffuse microcalcifications, certain collagen vascular disorders (especially systemic lupus erythematosus or scleroderma), and the inability to obtain clear margins of resection. In patients for whom mastectomy is appropriate, immediate reconstruction is considered.

For patients who undergo initial breast conservation therapy, lymphatic mapping is considered a reasonable alternative to axillary dissection and is preferred for patients who are clinically node negative.

Radiation therapy is used in all patients who undergo breast conservation therapy. Postmastectomy radiation therapy is recommended for patients with four or more positive lymph nodes after mastectomy or advanced stages of disease. Patients with stage II breast cancer and 1–3 positive lymph nodes may be offered postmastectomy radiation therapy on a selective basis. For additional information about radiation therapy, see chapter 9.

Systemic Therapy

The best time to develop adjuvant systemic therapy recommendations is after completion of initial surgical treatment and complete pathologic characterization of the tumor and regional nodes. Patients with highly favorable histologic subtypes (i.e., tubular, medullary, pure papillary, or mucinous) and patients with ductal and lobular carcinomas smaller than 1 cm have a lower risk of developing systemic metastases and may not require systemic therapy. These patients may consider hormonal adjuvant therapy alone if the tumor is estrogen and/or progesterone receptor positive. The precise role of tumor markers in this most favorable subgroup requires further study.

In patients with tumors of at least 1 cm or axillary lymph node involvement, cytotoxic adjuvant chemotherapy is appropriate. Typically, patients with positive lymph nodes are treated with adjuvant systemic chemotherapy consisting of a combination of 5-fluorouracil, doxorubicin or epirubicin, and cyclophosphamide and a taxane even if the tumor is hormone receptor positive. In patients with hormone-receptor-positive tumors, hormonal therapy is recommended after completion of cytotoxic chemotherapy. Postmenopausal patients with tumors between 1 and 2 cm and no axillary node metastases may be considered for hormonal therapy alone. Patients with T2 primary tumors and all premenopausal patients are treated with cytotoxic chemotherapy. For an excellent tool to assess the incremental benefit of cytotoxic, hormonal, and combined therapy go to http://www.adjuvantonline.com.

One of the important new additions to the systemic therapy arsenal is the use of "targeted" therapies. These are directed at specific molecular vulnerabilities of an individual tumor and typically require assessment of specific tumor features. Human epidermal growth factor receptor 2 (HER2) is overexpressed in 25–30% of breast cancers. This overexpression is most commonly the result of gene amplification. A number of studies have shown that breast cancers that overexpress HER2 have a more aggressive course and high relapse and mortality rates. Trastuzumab (Herceptin) is a humanized monoclonal antibody directed against the

extracellular domain of HER2. Single-agent trastuzumab has modest antitumor activity. In patients with HER2-overexpressing metastatic breast cancer, trastuzumab in combination with standard chemotherapies has demonstrated improvement in time to progression, overall response, duration of response, and survival compared to outcomes with the same chemotherapy alone. Other targeted therapies currently being tested in breast cancer clinical trials include gefitinib (Iressa; AstraZeneca) and erlotinib (Tarceva; Genentech), which inhibit the ErbB-1 tyrosine kinase; bevacizumab (a recombinant humanized monoclonal antibody to vascular endothelial growth factor receptor); and lapatinib (Tykerb; GlaxoSmithKline), a dual tyrosine kinase inhibitor that targets the epidermal growth factor receptor and HER2.

When radiation therapy is indicated (see "Local Treatment"), it is typically delivered after the completion of systemic therapy.

Surveillance

Follow-up is best performed by the team members who have cared for the patient. Follow-up visits include a detailed patient history and physical examination and selected screening tests. Mammography is performed 6 months after the completion of breast conservation therapy and annually thereafter. Chest radiographs are obtained annually in patients who have undergone breast conservation therapy. The role of more intensive surveillance has been questioned, and the current American Society of Clinical Oncology guidelines suggest that the data are insufficient to suggest the routine use of blood cell counts, automated chemistry studies, chest radiography, or other imaging studies. These guidelines also state that the routine measurement of CA15-3, CA27.29, or carcinoembryonic antigen for breast cancer surveillance is not recommended.

Wellness is important to all breast cancer survivors but is especially important to those with favorable, early-stage breast cancer. To this end, assessment of the impact of estrogen deficiency is particularly important. Assessment of skeletal and cardiac health is appropriate, particularly in patients with strong family histories of skeletal and cardiac problems. Quality-of-life issues due to estrogen deprivation, such as depression, hot flashes, weight gain, and vaginal dryness and atrophy, should be addressed symptomatically and preferably without the use of hormone replacement therapy. In patients who have not had a hysterectomy, yearly pelvic examinations are appropriate. Women receiving ongoing tamoxifen therapy may require endometrial biopsies. Sonography may be considered when women have vaginal bleeding or other symptoms. Assessment of bone mineral density is also appropriate, especially in patients receiving aromatase inhibitors, because of the propensity of these agents to accelerate skeletal demineralization.

Intermediate-Stage and Advanced-Stage Breast Cancer

One of the keys to the successful treatment of intermediate-stage and locally advanced breast cancer (see appendix, panel 3) is to obtain a detailed and accurate definition of the extent of disease prior to initiation of therapy. Most patients with intermediate-stage or locally advanced breast cancer are treated with initial (also called neoadjuvant or preoperative) chemotherapy, and in such patients, the initial pathologic description of the disease (extent of disease in the breast and the lymph nodes) is not available to guide the clinician in the subsequent decision-making process. Therefore, the decision whether breast conservation therapy is appropriate is based on a careful breast evaluation both before and after the completion of chemotherapy. Subtle skin involvement, attachment of the tumor to the underlying chest wall structures, and the presence of satellite lesions and multicentric tumors can affect whether breast conservation therapy is feasible. Radiologic or clinical evidence of tumor in the internal mammary, axillary apical, or supraclavicular nodal basins has an important impact on staging of the disease and on planning of local therapy. The systemic staging evaluation for patients with intermediate-stage and advanced-stage breast cancers is similar to that for patients with early-stage disease except that a bone scan and abdominal computed tomography or sonography are performed even in the absence of clinical symptoms or biochemical abnormalities.

Advanced Stage II and Stage IIIA Disease (Operable Disease)

Patients with T2 tumors larger than 4 cm (stage IIA) and those with T3 tumors but without fixed or matted axillary nodes (stage IIB and most stage IIIA cancers) are technically operable by classic criteria. Although total mastectomy with axillary lymph node dissection may be an acceptable initial treatment choice for patients with significant comorbid diseases, at M. D. Anderson preoperative anthracycline-based or taxane-based chemotherapy is often the preferred option for initial treatment. This permits observation for tumor response to the chosen regimen and allows some patients to subsequently undergo breast conservation therapy when mastectomy may have been required if surgery had been performed first. When breast conservation therapy is being considered, it is important to perform percutaneous insertion of radio-opaque markers in the tumor bed (typically using ultrasound guidance) to facilitate future localization and surgical resection.

For patients treated initially with mastectomy, adjuvant therapy using an anthracycline-based or taxane-based regimen is recommended for all patients who are medically fit. The decision-making paradigm for adjuvant systemic therapy for stage IIB and IIIA breast cancer is similar to that

outlined earlier in the chapter for earlier-stage disease. Hormonal therapy is used for at least 5 years if the tumor expresses hormone receptors. Postoperative radiation therapy is generally employed after the completion of chemotherapy. Breast reconstruction is appropriate for most women treated with mastectomy, although it is preferable to delay reconstruction until after the completion of local therapy for patients who will require irradiation.

A prospective multicenter trial is evaluating whether treatment with luteinizing hormone-releasing hormone agonists is feasible to preserve ovarian function in premenopausal women during the administration of adjuvant chemotherapy. This study includes only women who have hormonal receptor-negative disease.

Posttreatment follow-up for patients with advanced stage II and stage IIIA breast cancer is similar to the follow-up for patients with early-stage invasive disease.

Stage IIIB, Stage IIIC, and Selected Stage IVA Disease (Inoperable Disease)

Patients who have classically inoperable breast cancer (inoperable stage IIIA disease, stage IIIB and IIIC disease, and selected stage IVA disease) receive chemotherapy as initial therapy. It is inappropriate to attempt surgical intervention first in this patient group since the risk of positive surgical margins is high and extensive nodal disease may lead to a higher rate of complications. The use of initial chemotherapy in these patients has several potential advantages. Our preference is to use preoperative chemotherapy consisting of anthracycline-based or taxane-based regimens. Patients whose disease responds and becomes operable according to classic criteria (resolution of supraclavicular or matted axillary nodes, normalization of skin changes permitting complete surgical excision) are offered standard modified radical mastectomy. In patients whose disease responds dramatically, breast conservation therapy may become possible. Conversely, patients whose tumors demonstrate little or no response should be switched to a non-cross-resistant regimen before surgical therapy is attempted. Generally, all patients with advanced breast cancer undergo irradiation of the breast or chest wall and regional nodes, and thus immediate reconstruction is discouraged. Posttreatment follow-up for patients with initially inoperable breast cancer is similar to the follow-up for patients with early-stage invasive disease.

We have recently opened an Inflammatory Breast Cancer Clinic specifically for patients with inflammatory breast cancer. These patients have a defined imaging evaluation prior to clinical evaluation and are evaluated by a team of medical, surgical, and radiation oncologists. The goal is to facilitate integrated multimodality treatment with new investigational approaches in this group of patients with a highly aggressive type of breast cancer.

Local-Regional Recurrences and Systemic Metastases

The assessment and treatment of patients with local-regional recurrences or systemic metastases (see appendix, panels 4 and 5) depends in some measure on the particular clinical scenario. Global assessment includes chest radiography, radionuclide bone scan, computed tomography of the abdomen, complete blood cell counts, and liver function tests. It is important to have confidence that the diagnosis is correct, so it is usually appropriate to obtain histologic confirmation of the recurrence or metastasis—usually by fine-needle aspiration or core biopsy—and to perform hormone receptor and Her-2/*neu* assays on the specimen.

Local-Regional Recurrence

When the staging work-up fails to reveal any evidence of visceral metastasis and tumor is encountered only in the breast, the chest wall, or the regional nodal basins, it is appropriate to embark on a curative course of therapy. Complete imaging of the disease using mammography, sonography (including regional nodal assessment), and possibly computed tomography should be performed before treatment is initiated.

Most patients who have a recurrence after breast conservation therapy require completion mastectomy as their local therapy. Initial chemotherapy may be considered in patients with invasive disease whose tumor is not initially resectable. When the breast has not previously been irradiated (usually after surgery alone for DCIS), re-excision of the recurrent lesion followed by irradiation may be considered. Adjuvant systemic therapy is generally recommended after local recurrence of invasive cancer because of the high risk of subsequent metastasis.

While local-regional recurrences after mastectomy can occasionally be managed using initial surgery, it is common to find that the disease is too extensive to be completely encompassed within a reasonable surgical field. In the case of numerous cutaneous nodules or extensive nodal disease, initial chemotherapy is the preferred approach. The choice of agents is based on the type of chemotherapy previously used, the interval since prior systemic therapy, and the tumor receptor status. Once a sufficient response is achieved, residual disease is surgically excised. Patients who have not previously had radiation therapy undergo irradiation.

Systemic Metastases

The therapeutic goal for patients with documented visceral metastases is prolongation of survival and enhancement of quality of life. Since current approaches do not appear to be curative, it is important to balance therapeutic efficacy with treatment-related toxicity. Thus, when the tumor is

positive for estrogen or progesterone receptors and the patient is symptom free, hormonal therapies are the preferred initial therapy. Clinical scenarios especially suited to hormonal therapy include disease limited to bone or soft tissue and limited, asymptomatic visceral disease. In premenopausal women, tamoxifen is the preferred initial hormonal therapy in patients not previously treated with this agent. In postmenopausal women with prior tamoxifen exposure, aromatase inhibitors, fulvestrant, progestins, or androgens can be employed. When the tumor responds to this initial hormonal maneuver, as evidenced by tumor shrinkage or long-term stabilization of disease, second-line hormonal therapy should be considered at the time of subsequent progression.

Cytotoxic chemotherapy is indicated for patients with hormone receptor–negative tumors, patients with hormone-refractory disease, and patients with symptomatic visceral metastases, regardless of hormone receptor status. A variety of regimens are considered appropriate, including 5-fluorouracil, doxorubicin, and cyclophosphamide combination therapy or taxanes in patients who have not been exposed to these agents and trastuzumab in patients with tumors that overexpress Her-2/*neu*. Patients should be encouraged to participate in clinical trials when appropriate. Supportive care should be considered when disease fails to respond to two sequential chemotherapy regimens or if the patient's performance status deteriorates to Zubrod 3 or greater.

High-dose chemotherapy and bone marrow or stem cell rescue is considered investigational for patients with systemic metastases. Patients with systemic metastases considering this therapy should be treated in the context of a clinical trial.

Frequently, patients with metastatic breast cancer develop specific clinical scenarios for which surgery, radiation therapy, or regional chemotherapy may be indicated. These include brain metastases, spinal cord compression, painful bone lesions, pathologic fractures, plexopathy and radiculopathy, and pleural effusions.

Conclusions

The M. D. Anderson approach to the treatment of breast neoplasms is centered on optimizing the effectiveness of therapy while minimizing the acute and long-term impact of treatment. Accurate definition of the disease, careful assessment of the treatment options, and consideration of the needs and wishes of the patient and his or her family are prerequisites for superior care. While the guidelines outlined in this chapter describe the best standard care that we believe can be justified by proven clinical science, many patients at M. D. Anderson elect to have part or all of their care

delivered in the context of ongoing clinical trials. Participation in clinical research gives patients the opportunity not only to receive state-of-the-art cancer care but also to potentially be the first to receive tomorrow's treatment today and to contribute to the betterment of breast cancer care for future patients with this disease.