Innovations in Breast Cancer Care
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ABSTRACT

PURPOSE: To examine the treatment of breast cancer from a historic perspective and explore current therapies and innovations in diagnosis and treatment.

EPIDEMIOLOGY: In 2003, 212,600 new cases of breast cancer were diagnosed, and it is estimated that more than 40,000 of those cases will be fatal. The probability of developing invasive breast cancer is age-dependent, ranging from a 1 in 225 (0.44%) chance for women younger than 39 years to a 1 in 14 (7.02%) chance for women aged 60 through 79, with an overall 1 in 8 (12.83%) lifetime risk.

REVIEW SUMMARY: From early in recorded history, women and their physicians have been plagued by breast cancer. Currently, breast cancer remains a leading cause of death in women, second only to lung cancer. The treatment paradigm has shifted from one mandating radical excision of the breast and all surrounding tissue, to a more systemic view whereby as much breast tissue as possible is conserved and adjuvant therapy is offered to prevent metastasis. Advances in treatment have accelerated over the last few decades and have led and will continue to lead to significant improvements in mortality and morbidity. This article examines an approach to breast cancer management that considers the specific circumstances of each individual woman, guided by tumor biology, age, competing risks of death from other comorbidities, and personal preferences in which survivorship issues have assumed tremendous importance. Finally, future directions in breast cancer care are discussed.

TYPE OF AVAILABLE EVIDENCE: Randomized-controlled trials, prospective cohort studies, systematic reviews.
GRADE OF AVAILABLE EVIDENCE: Good to excellent.

CONCLUSION: Physicians and patients now may select from a myriad of treatments for breast cancer, including surgery (mastectomy vs lumpectomy), radiation therapy, chemotherapy, hormonal therapy, and other biologically targeted therapies. In the future, molecular and imaging markers in combination with clinical parameters will help individually characterize breast cancer type, predict response to therapy, determine prognosis, and ultimately dictate the informed treatment choices women make in conjunction with their physicians.


Breast cancer is the most commonly diagnosed cancer among American women and the second most common cancer-related cause of death in women—surpassed only by lung cancer. In 2003, 212,600 new cases of breast cancer were diagnosed, of which an estimated 40,000+ will end in mortality. The probability of developing invasive breast cancer is age-dependent, ranging from a 1 in 225 (0.44%) chance for women under age 39 to a 1 in 14 (7.02%) chance for women aged 60 through 79, with an overall 1 in 8 (12.83%) lifetime risk. Although the annual incidence of breast cancer has increased during the last decade from 180,000 to 211,000 cases, in 2003 the mortality rate decreased from 45,000 to 39,000 cases. The probability of developing invasive breast cancer is age-dependent, ranging from a 1 in 225 (0.44%) chance for women under age 39 to a 1 in 14 (7.02%) chance for women aged 60 through 79, with an overall 1 in 8 (12.83%) lifetime risk.
Our knowledge of breast cancer dates back almost as far as recorded history, with the first known description of a “bulging tumor of the breast” noted on an Egyptian papyrus from Thebes in 1600 BC. Surgery was practiced without benefit of antibiotics or anesthetics, and was thought to carry a high risk of morbidity and poor prognosis. Other early treatments included topical therapies, specialized diets, and even exorcisms. In 200 AD, Galen described breast cancer as caused by an excess of black bile, and this theory dominated medical philosophy and practice for 1600 years.

Mastectomy was described during the Roman period by Celsus as well as by Leonides, a second-century Greek philosopher. Until the 19th century, breast cancer surgery was limited to burning the “lesions” with cautery or performing amputations with guillotine-like instruments. Then, in the late 1800s famed surgical pioneer William Halstead purported that, “Breast cancer [was] a local disease that spread through contiguous extension and throughout the body in [a] predictable centrifugal manner along the lymphatic.” In other words, cancer began locally and then spread to the lymphatics, which facilitated invasion of distant organs. In 1890, Halstead published a description of the radical mastectomy that would become the basis of surgical therapy for the next 100 years. The operation involved a wide excision of skin later requiring coverage with a skin graft. Routine were removal of the pectoralis muscle, radical axillary lymph node dissection, and excision as en bloc dissection, “cutting as wide as possible on all sides of the growth.” Today, the Halsted radical mastectomy is considered a disfiguring surgery, but when first introduced it was a major advance in the attempt to treat and cure women whose cancers had been previously ignored. In fact, until the 1950s or early 1960s, surgical approaches would become progressively more extensive, involving even greater tissue resection. These aggressive procedures were associated with significant morbidity, the most debilitating being lymphedema.

Bernard Fisher often is credited with ushering in the modern era of breast cancer treatment. Fisher founded a clinical trial cooperative group, the National Surgical Adjuvant Breast and Bowel Project (NSABP), which gathered surgeons and oncologists in the United States and Canada to participate in clinical oncology studies. Between 1957 and 1970, the NSABP conducted a number of landmark trials that changed breast cancer management and promulgated the advantages of modified radical mastectomy. Fisher's research was instrumental in formulating a paradigm shift by suggesting that breast cancer might be systemic early in its inception, with disseminated cancer cells possibly the cause of potential metastases. Fisher collected data from randomized clinical trials and demonstrated that breast-conserving surgery combined with radiation resulted in survival rates equivalent to those of mastectomy; moreover, such results could be accomplished with decreased morbidity. Further, he established that systemic therapy was an important treatment consideration for most breast cancer patients.

Interestingly, Fisher was not the first physician to advocate breast conservation. After World War II, surgeons began to question radical mastectomy as mammography allowed the clinical detection of increasingly smaller tumors. Improvements in radiation, chemotherapy, hormonal therapy, and increasing patient advocacy led surgeons such as George Crile, Jr, and Oliver Cope to advocate lumpectomy beginning in the mid 1950s.

In 1971 and 1976, respectively, 2 landmark randomized clinical studies were conducted to examine alternative local and regional treatments of breast cancer. The NSABP B-04 trial enrolled 1665 women. Study subjects were treated either with radical mastectomy or total or simple mastectomy (with preservation of pectoralis muscles and axillary nodes) with or without accompanying regional irradiation. Axillary lymph node dissection was performed only if nodes were subsequently positive for tumor cells. There were no significant differences among the 3 groups of patients with clinically negative axillary lymph nodes with respect to disease-free survival, distant disease-free survival, or overall survival (follow-up was 5, 10, 20, and 25 years). Similarly, in the node-positive group, there was no difference between those who underwent radical vs simple mastectomy without axillary node dissection but with regional irradiation.

The NSABP B-06 trial, which took place 5 years later, compared lumpectomy with total mastectomy in subjects with a clinical tumor size ≤4 cm. The treatment arms were: (1) total mastectomy plus axillary node dissection; (2) lumpectomy plus axillary node dissection; and (3) lumpectomy plus axillary node dissection and radiation. In addition, patients with positive nodes received chemotherapy. Total mastectomy was performed in the event of ipsilateral breast tumor recurrence. No difference in survival was found, even after 25 years, demonstrating again that mastectomy did not impact overall survival. There are a total of 7 randomized trials from around the world showing that lumpectomy plus radiation therapy compared with mastectomy are equivalent in terms of impact on survival. Figure 1 illustrates the difference between radical mastectomy and total skin-sparing mastectomy.

With increasing options to treat and prevent death from breast cancer, increased focus and effort was put into early diagnosis. Earlier stage breast cancer was more easily treated with better survival and better surgical options. Thus, mammography or radiographic imaging of the breast emerged as a tool for improving diagnosis and for screening.
CURRENT DIAGNOSTIC OPTIONS

MAMMOGRAPHY

Mammography currently is the most widely used screening tool for breast disease. Based on a meta-analysis of randomized trials that began in the 1980s, it has been concluded that mammography affords a relative risk reduction in breast cancer mortality of 20% to 30%, although the benefit to a woman who is diagnosed with breast cancer is an absolute reduction of about 4% to 6% in mortality. Benefits are greater in the population between the ages of 50 and 70 where breast cancer is more prevalent. Most organizations in the United States have guidelines that recommend annual screening mammography for all women aged 40 to 70. At this time, no other test is recommended as a screen for breast cancer, although there remain important ways in which mammography can be improved. Investigators are now considering alternative ways in which mammography can be routinely applied to the general population to target those women most likely to derive benefit from the test. Initiatives are under way to encourage centralized review of mammograms. Future advances in molecular medicine could help identify those women at higher risk who would benefit most from mammographic screening.

ULTRASOUND AND MAGNETIC RESONANCE IMAGING

Ultrasound and magnetic resonance imaging (MRI) are 2 other tools that have become established in the breast imaging armamentarium. The primary role of ultrasound remains the characterization and localization of breast lesions. As such, it is an ideal tool for image-guided biopsy. MRI is an increasingly accessible technology that is useful for defining the extent of disease and monitoring response to therapy. It also appears to have a role in screening high-risk women who are known or suspected carriers of a BRCA mutation. However, MRI is not currently recommended for general screening due to its low specificity, expense, and lack of localization tools.

Diagnostic techniques continue to evolve in breast cancer screening and imaging—important steps that go hand in hand with the ability to offer less invasive treatment for tumors discovered at earlier stages. For example, the development of genetic screening has facilitated intensive screening for those truly at risk based on inherited susceptibility in the BRCA1 and BRCA2 genes, helping clinicians determine which patients may benefit from increased surveillance and/or preventive interventions. For those women who carry mutations and have a risk of breast cancer at a young age, screening with mammography may not be optimal given the lower sensitivity in very dense breast tissue that is more common among young women. In this instance, MRI appears to be of value. However, hereditary breast cancers are believed to represent only a small proportion (5% to 10%) of all breast cancers, and the prevalence of BRCA1 in the general population is 0.1%.

Increased scrutiny identifies many lesions that, upon examination of biopsy, may turn out to be benign or worse, precancerous. Finding precancerous lesions may not always be a boon because many of them might not otherwise come to clinical attention. Thus, inappropriate screening with the wrong types of tests in low-risk groups may be of little value and/or result in false positives and overtreatment. Thus, as more sophisticated screening tools are developed, they must be accompanied by criteria for appropriate use and interpretation.

A number of advances, including digital mammography, may change how we apply wide-scale screening. Other novel approaches to screening currently are in development and include the use of serum-based screening of proteins (proteomics) and blood-based testing to look for variation in inherited genes (single nucleotide polymorphisms).

MANAGEMENT OF BREAST CANCER

Greater public awareness and widespread screening have enabled the earlier identification of lesions and resulted in a higher lumpectomy rate. Some women have extensive local disease or multifocal disease and are not candidates for breast conservation. Others, although not the majority, prefer mastectomy to lumpectomy and radiation therapy. The most important point to stress, however, is that there is usually a choice of procedure for local control. If mastectomy is to be considered as an alternative to breast conservation, reconstruction—either immediate or delayed—also should be provided as an option. Immediate reconstruction and other significant advances in reconstructive surgery, including skin sparing, nipple sparing, and deep inferior epigastric perforator muscle-sparing flaps, have dramatically improved...
cosmesis, making this alternative far more acceptable as an option to prevent local recurrence.\textsuperscript{29,30}

Increasingly, many choices are available for the management of breast cancer. Questions and controversies still remain, especially with respect to the management of axillary nodes, the most appropriate treatment for preinvasive disease, and the use of adjuvant therapy for early lesions.

**Evaluating the Extent of Disease by Lymphatic and Hematogenous Spread**

Surgical evaluation of the axillary lymph nodes is critical as nodal status remains the single most important prognostic indicator for breast cancer patients.\textsuperscript{34} For most patients with involved nodes, levels I and II axillary lymph node dissection (ALND) are sufficient, with less morbidity than a level III ALND (Figure 2), excellent accuracy of staging (2\% to 3\% error rate), and no difference in survival.\textsuperscript{35} The value of information regarding nodal status and potential for long-term locoregional control must be weighed against the morbidity of the procedure, which includes postoperative pain, lymphedema (10\%-30\% incidence rate), decreased arm mobility, and potential nerve or blood vessel damage. Newer techniques, such as sentinel lymph node dissection (SLND), allow a more minimal intervention with less morbidity.

Following an early study of lymphatic mapping for melanoma, Morton and Giuliano performed 174 lymphatic mapping procedures, injecting a dye at the primary tumor site to follow it to the sentinel node. The sentinel node was selectively removed prior to performance of standard ALND. Accuracy improved as the surgeon became more experienced at the procedure, with 100\% accuracy in the last 87 procedures. In the last 54 of the 174 mapping procedures, the anatomic level of the sentinel node was recorded. The sentinel node was identified in 43 of these 54 cases and in 10 of 43 (23.7\%) examined, the sentinel node was a level II axillary node, and would have been missed had only a level I dissection been performed.\textsuperscript{36}

Another technique for identifying sentinel lymph nodes (SLNs) is the use of a colloid labeled with the technetium-99 isotope, and a number of large studies have shown this technique to be very accurate, particularly in the hands of an experienced surgeon.\textsuperscript{37} Veronesi et al found that, for surgeons who routinely perform SLND, the procedure is quite specific, in the range of 98\% to 100\%, with a sensitivity of 95\% to 98\%.\textsuperscript{38}

As of this writing, several large-scale US studies designed to further define the role of SLND in early-stage breast cancer have just completed accrual and will provide data on survival and morbidity of SLND and ALND. In a design similar to the Italian SLN randomized trial by Veronesi et al, the NSABP B-32 trial randomized patients to SLND plus ALND vs ALND only if the SLN was positive. This trial, studying 10-fold more patients than the Veronesi trial (5611 women), has evaluated the accuracy of SLND compared with ALND and we are awaiting the impact on survival.

As part of the NSABP B-32 trial, hundreds of surgeons across the country were trained to perform SLND. The technical results demonstrated that the SLN can be readily identified, with a technical success rate of 97\%.\textsuperscript{39} This improves with surgeon training, is slightly better in women under age 50 as compared with those over 50, and slightly lower (95\%) in T3 lesions. Approximately 26\% of patients had positive SLNs, but only 0.6\% had positive lymph nodes outside the axilla. If a sentinel node was positive, the chance of finding other positive nodes was 38\%. The false-negative rate was 9.7\%. This means that the test is very reliable in women with a very low likelihood of having positive nodes, but not as reliable where there is a high probability of having positive nodes. The false-negative rate goes down when more sentinel nodes are found, and is significantly lower if a needle biopsy is used for diagnosis rather than an excisional biopsy (8\% vs 15\%, respectively). The false-negative rate does not improve with surgeon training. The technical results show that this is a feasible procedure, and the early results of the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial (designed to study quality of life in women undergoing SLND vs ALND)\textsuperscript{40,41} show that SLND is indeed less morbid and better tolerated than axillary dissection.

The American College of Surgeons (ACS) trial, ACOSOG Z0011, a randomized trial of ALND vs no ALND in women with breast cancers <5 cm and with positive SLNs, was begun in order to determine if there

**Figure 2. Axillary Lymph Node Dissection Levels**

A) axillary lymph nodes, levels I; B) axillary lymph nodes, levels II; C) axillary lymph nodes, levels III.

* Illustration © Mary K. Bryson 2005.
is a survival benefit associated with removing the rest of the axillary basin in node-positive patients when receiving adjuvant therapy. Unfortunately, this trial has been suspended due to low accrual; hopefully, some important information will still be gathered from the patients already participating.

ACOSOG Z0010 is a registry of patients undergoing SLND to assess SLN identification rates as well as short- and long-term morbidity. What differentiates this trial from NSABP B-32 is that surgeons participating in this observational study demonstrated their proficiency by performing 20 SLNDs followed by ALND with a 95% identification rate and less than 5% false-negative rate. Comparison of technical results of the 2 trials should be forthcoming. SLND generally involves excision of only 1 to 3 lymph nodes, compared with an average of 10 to 30 in traditional ALND. Thus, it may be performed on an outpatient basis and is associated with fewer side effects, including lymphedema rates of between 1% and 2%. In addition, the pathologist is able to more carefully examine the nodes in question. Since fewer nodes are evaluated, the pathologist can look at several slices through each sentinel node rather than just 1 slice in the middle of the node. SLND is becoming established as the standard of care for determining whether cancer is present in the axillary lymph node basin. This technique is one of the significant advances in providing less morbidity to women with breast cancer.

As with any new technology, controversies still exist with respect to the role of SLND. SLND has no role in ductal carcinoma in situ (DCIS) unless a mastectomy is being performed. Pathologic evaluation using immunohistochemistry should not be performed until there are data to show an adverse outcome if pathologists find microscopic foci of disease not visible with standard light microscopy. The role of SLND in patients who have undergone neoadjuvant chemotherapy has been found to be accurate in experienced hands.42

**Bone Marrow Micrometastasis**

An area of active research and debate is the role of bone marrow testing for the determination of prognosis and possible treatment in breast cancer. This assay has been studied for many years and has now been adopted in Germany. A team of physicians led by Braun et al used cytokeratin antibodies targeting epithelial cancer cells to examine the clinical significance of circulating tumor cells (CTCs). The researchers sought to determine whether CTCs in the bone marrow were predictive of prognosis in women with stage I, II, or III breast cancer.43 Bone marrow aspirates were obtained and analyzed from 552 women with cancer and 191 control subjects. Cytokeratin-positive cells were detected in the bone marrow specimens of 2 of the 191 (1.05%) control patients vs 199 of the 552 (36%) women with malignancies. After 4 years, disease progression was examined. It was found that the presence of micrometastasis in the bone marrow did not necessarily correlate with the presence of lymph node status.

Interestingly, bone marrow micrometastases were associated with the occurrence of clinically overt distant metastasis and death from cancer-related causes. Specifically, of 199 patients with occult malignant cells, 49 died of cancer (24.6%) compared with 22 of the 353 without these cells (6.2%). The authors concluded that the prognostic significance of CTCs equals that of lymph node status, and the presence of both was significantly worse than either alone. This study is significant in that it suggests that CTCs would serve as a tool to refine decisions regarding systemic therapy.44

A test for CTCs may become useful for monitoring the persistence of risk for metastatic disease and may enable the application of novel interventions in high-risk adjuvant patients. A recent study has demonstrated that CTCs in the peripheral blood in patients with metastatic disease are a sensitive, prognostic and predictive marker. The absolute number has prognostic value since those with high numbers had a much shorter survival. It is predictive in that the short-term change in response to therapy was a strong indicator of the degree and duration of benefit from the therapy.45 CTCs are much more readily detected in peripheral blood of patients with metastatic disease, particularly compared with the setting of primary cancer. The bone marrow is a much more sensitive assay for CTCs in a primary tumor. However, before this test can be broadly used, it is critical that standards for reproducible identification of CTCs be established.46

**Special Considerations for Ductal Carcinoma In Situ**

Perhaps the least understood entity in breast cancer today is DCIS. Between 1983 and 1992, the incidence of DCIS increased by 500%, and currently almost 56 000 new cases are diagnosed annually in the United States. Despite the fact that DCIS is considered a precursor, increased detection of DCIS has not been shown to impact the incidence of invasive carcinoma.1 By definition, DCIS refers to cancer cells that are detected and confined within the milk ducts of the breast without invasion of the surrounding parenchyma or lymph nodes (Figure 3). DCIS is considered by many to be the earliest form of cancer; others have characterized DCIS to be a “precancer” or “stage 0 cancer.” DCIS confers an excellent prognosis, with a 10-year survival rate of 98% to 99%.48

Currently, the standard of care for DCIS is variable, depending on the subtype of ductal cancer present; high-grade lesions or those that have comedonecrosis tend to behave more aggressively. However, a number of other factors influence the chance of recurrence and therefore treatment choice: size of the lesion, age at diagnosis, and extent of surgical excision relative to the size of the DCIS.

Treatment options include surgery (ie, mastectomy or lumpectomy), radiation therapy, and/or hormonal
therapy, usually with tamoxifen. Although mastectomy provides the lowest local recurrence rates (1%-2%), this procedure most commonly is reserved for large lesions or multicentric disease.

Multiple trials are evaluating the role of adjuvant therapy for DCIS. In one prospective randomized trial, NSABP B-17, Fisher et al found an approximately 50% reduction in risk of progression (defined as ipsilateral breast tumors) when radiation therapy (XRT) was employed following lumpectomy in a cohort of 573 patients.57

Risk may be further reduced via the use of tamoxifen, a nonsteroidal antiestrogen, as evidenced by the results of another NSABP B-24 study, in which 1804 women with DCIS who had been treated with lumpectomy and XRT were randomized to tamoxifen or a placebo. In this setting, adjuvant tamoxifen was found to reduce the likelihood of recurrence by 30%.58 A subsequent retrospective review of the tissue blocks from this study suggested that tamoxifen benefit is limited to women who have estrogen receptor (ER)-positive disease.51 At median follow-up at approximately 6 years, women in the tamoxifen group had fewer breast cancer events than did those taking placebo. Based on these and similar studies, the general guidelines for treatment of DCIS include consideration of both radiation and tamoxifen in women undergoing lumpectomy. Understanding the underlying absolute risk of recurrence of DCIS and the risk of progression to invasive cancer will accelerate our ability to find innovative strategies for testing the reversibility of in situ lesions.52 A window of 2 to 3 months after detection is permissible and may provide the optimal scenario for studying the biology of DCIS lesions and their responsiveness to established and novel agents.53

THE ROLE OF SYSTEMIC THERAPY

HORMONE THERAPY

Decades of clinical trials have established the critical role of systemic therapy in reducing the risk of death from breast cancer. The meta-analysis from the Early Breast Cancer Trialists’ Collaborative Group had an enormous influence on standardizing chemotherapy guidelines for women with breast cancer and has established the role of doxorubicin hydrochloride-based regimens as first-line therapy. Our current paradigm assumes that all patients have some risk for disease progression, and the benefits of adjuvant therapy50,55 are presumed to apply to everyone. In common clinical practice, systemic therapy usually is prescribed for patients whose tumors are >1 cm and for those with nodal involvement.50,55 Additional improvements in survival have now been established through the addition of taxanes and dose-dense regimens (eg, administering drugs at more frequent intervals).56-62 The existence of mature outcomes from many randomized trials combined with large tumor registry data has enabled the development of computerized tools to predict the absolute benefit of systemic therapy for patients based on tumor size, grade, lymph node status, patient's age, comorbidities, and ER status.57 One such tool, available free online (www.adjuvantonline.com) and updated every 6 months, has been found to predict mortality accurately within 2%58 and is increasingly used by oncologists worldwide.

Hormonal systemic therapies really are the first example of tailored therapy for breast cancer. ER expression in breast cancer predicts the benefit from hormonal therapy, because it is a prerequisite for the use of endocrine therapy to disable hormone-dependent tumor cell proliferative and survival pathways. Tamoxifen, which has been used to block ER activities in tumors, has been in standard use for 30 years and likely is responsible for significant improvements in survival of breast cancers.64 A new class of hormonal agents has been introduced recently for postmenopausal women. These drugs function by blocking aromatase inhibitors. During the last 3 years, a number of critical studies have matured, including a 9000-patient trial comparing the aromatase inhibitor anastrozole with tamoxifen and or with the combination of the 2 (the Anastrozole, Tamoxifen Alone or in Combination trial). Anastrozole had a superior outcome in terms of both local and distant recurrence.65 Similarly, letrozole has been shown in the neoadjuvant setting to be more effective than tamoxifen, particularly in human epidermal growth factor receptor-2 (HER-2)-positive tumors.66 Importantly, it has been shown that aromatase inhibitors can be taken after 5 years of therapy with tamoxifen, and recurrence and death from metastases can be reduced by 50% in hormone receptor-positive patients who have not relapsed.67 However, about 50% of ER-positive tumors treated in the adjuvant setting are destined to relapse with metastatic disease despite endocrine intervention. Important areas for future research will be the elucidation of the pathways by

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**Figure 3. Breast Cancer Progression**

Ductal structures are lined with epithelial cells. When cells begin to proliferate and pile upon each other, the process is considered hyperplastic. As the cells begin to show variation, they are considered “atypical.” In the in situ process, the cells themselves resemble cancer cells; however, they are confined to the ducts and the basement membrane is intact. When the “cancerous” cells break through the basement membrane and invade the surrounding tissue, the process is considered invasive cancer.
which these tumors escape hormonal agents and the
design of agents to specifically target those pathways.

**POLYCHEMOTHERAPY AND BIOLOGICALLY TARGETED THERAPIES**

Other biologically based therapies are being developed and tested for the treatment of breast cancer. A comprehensive review of these is beyond the scope of this article; however, the hope for molecularly targeted agents has been fueled by the development of drugs such as trastuzumab. The identification of HER-2/neu on the cell surface as a marker of poor prognosis led to the development of the humanized HER-2–targeted antibody, trastuzumab. The success of the trastuzumab trials in extending survival in the metastatic setting is considered to be indicative of how specific molecular abnormalities, the up-regulation and overexpression of HER-2/neu, can be used as a basis for targeted therapy. Trastuzumab has now been added to standard chemotherapy in 2 randomized trials in the adjuvant therapy setting. Both trials met the early stopping rules for ending the trial because of the dramatic reduction seen in disease-free survival by the addition of trastuzumab to concurrent chemotherapy. The combined cardiac toxicity analysis for these trials (trastuzumab in combination with taxane following doxorubicin + cyclophosphamide) showed that there was a 4% incidence of congestive heart failure (all women had normal cardiac function at the start of the trial), all successfully treated, and no excess of cardiac deaths in the treatment arm. Another European trial, the HERA trial, is testing the impact on survival of trastuzumab given after chemotherapy (any type) for 1 or 2 years. Preliminary results demonstrate that 1 year of herceptin alone after chemotherapy compared with no trastuzumab also significantly reduces recurrence in the population of women with HER-2–positive tumors. Whether trastuzumab alone is as good as trastuzumab + chemotherapy concurrently is not yet known, because the patient populations are different and follow-up is fairly short. In the NCCTG-N9831 trial, trastuzumab alone after the completion of chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) was compared with trastuzumab given concurrently with chemotherapy (doxorubicin and cyclophosphamide followed by trastuzumab + paclitaxel), and early results suggest that the combined therapy is superior; however, it is simply too early to know definitively. As these data mature, these critically important trials will contribute a great deal to our knowledge of how to treat HER-2–positive breast cancer. Fortunately, we will have the opportunity, over the next few years, to focus on ways to optimize the delivery of molecularly targeted agents, maximizing benefit and minimizing toxicity. The trials show that women with HER-2–expressing tumors have a worse survival and that recurrence and death are early events in such tumors, allowing appreciation of the impact of targeted therapy.

Clearly these trials represent the potential of targeted biologic therapies to dramatically change the outcome of women with breast cancer. Trastuzumab represents a great advance, but all patients with overexpression do not necessarily respond to trastuzumab, either alone or in combination with chemotherapy. New mechanisms to explain this are being sought, and other HER-2/neu–targeted therapies are in development.

The HER-2 story also reinforces the notion that reversing metastatic disease will remain a very significant challenge for some time to come, but the potential for cure is much greater if the agents can be applied to women at risk for progression prior to the diagnosis of metastatic disease, in the adjuvant or neoadjuvant setting. A method for accelerating the testing of new agents may be the setting of neoadjuvant therapy. By treating larger tumors with systemic therapy prior to surgery, it is possible to measure the response of the primary tumor to standard therapy. A number of investigators have used this as a platform to test new agents, develop tools to identify those with a relatively poor response to therapy early in the course of care, and use molecular fingerprinting to generate clues to guide the introduction of new targeted agents in the future.

**THE ROLE OF NEOADJUVANT THERAPY**

Breast cancer treatment traditionally follows a standard delivery scheme: surgical removal; chemotherapy; radiation therapy; and hormone therapy, if appropriate. However, it is becoming increasingly clear that the order of therapy may not have an impact on patient survival. Understanding the impact of systemic therapy on the primary tumor is difficult when administration takes place after the tumor has been removed. Therefore, reordering therapies allows for evaluation of their impact on the primary tumor. Guidelines for administering systemic therapy currently are based on the results of randomized clinical trials and are primarily driven by recommendations from Oxford Overview Analysis, the National Institutes of Health Consensus conference, and the St Gallen Consensus meetings. However, such recommendations presume that breast cancers vary only on the basis of tumor size and lymph node burden and thus should be treated similarly. Emerging molecular tools enable characterization of tumors based on genes and protein expression; to improve our ability to target therapy and improve outcomes, we need to understand this genetic information in the context of a patient’s response to therapy. By characterizing tumors and treating patients using the adjuvant approach, information will continue to emerge. Perhaps a better strategy is the use of the neoadjuvant paradigm to individually tailor therapies. The primary tumor can then be used as a surrogate marker of response. Nesting neoadjuvant treatment and correlating patient and cancer marker studies into outcome trials provides an opportunity to optimize treatment regimens that can then be tested in randomized trials.
Historically, preoperative or neoadjuvant chemotherapy was utilized in women with inflammatory or inoperable breast tumors. Preoperative chemotherapy was reserved for endocrine-treatment–induced down-staging of inflammatory or unresectable tumors in elderly patients, and combination chemotherapy administered in the neoadjuvant setting followed by surgery, radiation, or both was introduced in the mid to late 1970s at MD Anderson Cancer Center for patients with stage IIIA and IIIB cancers. The majority of patients showed tumor shrinkage in response to chemotherapy. Patients with complete remission after chemotherapy had far better outcomes than those with partial remission. Those with no change after chemotherapy had the worst survival rate, with nearly 90% mortality after 6 years of follow-up. Various researchers conducted prospective trials of multimodality neoadjuvant therapy for women with locally advanced cancers, demonstrating a partial response to systemic chemotherapy in 60% to 70% of patients and a complete clinical regression of the local tumor in 25% to 30% of patients. The Milan group conducted 2 prospective trials with a total of 277 patients and a 10-year follow-up; they reported improved outcomes among patients who had smaller initial tumor burden (size and node status), longer duration of chemotherapy, and multimodal therapy (radiation, chemotherapy, and surgery). They established that surgical excision—either breast conservation or mastectomy—improved local control, but reaffirmed that control of systemic disease continued to be the main problem for patients with locally advanced cancer. The Paris group reported similar findings in their trial of 250 women. In addition, they studied the use of breast conservation after initial tumor shrinkage with chemotherapy and found that the breast preservation rate was 94% at 5 years. They concluded that breast conservation following neoadjuvant therapy was safe and, moreover, neoadjuvant therapy could increase the likelihood of breast conservation.

A recent consensus conference concluded that the order of therapy is not important in determining the outcome but can help determine which regimens are most efficacious. It is possible that some women may benefit greatly from adjuvant therapy, whereas some may not benefit at all. These data suggest that in the future treatments should be tailored to individual patients. By identifying women who do not benefit from treatment, there is an opportunity to identify markers and mechanisms of resistance and to use novel therapeutics for these women. The neoadjuvant setting provides a forum to rapidly design and test new treatment strategies.

The Evolving Role of Radiotherapy

Radiation therapy plays a major role in the treatment of breast cancer. As discussed earlier, the addition of radiation to lumpectomy has made local control after breast conservation similar to local control with mastectomy. Radiation is thought to improve survival in cases of more locally advanced cancer; it also is recommended as part of standard therapy for women with tumors >5 cm or with ≥4 involved nodes, regardless of the type of surgery performed. Recent trials suggest there also may be a survival advantage in node-positive premenopausal women.

For women with more localized disease, new techniques and stratification of therapy are being considered, either by identifying a population that benefits very little from radiation or through the introduction of partial breast irradiation (ie, intraoperative radiotherapy, brachytherapy, and placement of short-term intracavitary devices). Another option is shortened external beam regimens, with an eye toward reducing morbidity and the extent of treatment.

The Role of Age and Biology

A white woman in the United States has a 1 in 8 chance of developing breast cancer. However, in terms of true breast cancer risk this statistic refers to lifetime risk if a woman lives to be 85 years. A 40-year-old woman has a 1.5% chance of developing cancer over the next 10 years, and a 0.2% chance of dying of breast cancer. Fifty percent of women diagnosed with breast cancer are older than 65 years, and these women have a 60% chance of dying from another cause. As our sophistication in analyzing the biologic behavior of tumors improves, we are likely to find that the distribution of cancers in the older population is likely to be much more weighted to more indolent types of cancers. Molecular tools will be increasingly available to characterize the risk of recurrence associated with the tumors we detect. In the future, we will need to assess the competing health risks and make sure that our interventions do not simply add morbidity.

DCIS is one example in which the concept of competing risk may play an important role in defining appropriate healthcare decisions. Since DCIS tends to be slow progressing, determining aggressiveness of treatment may depend partly on the age of the patient at disease development and whether there is another competing risk for mortality.

For instance, if a 60-year-old patient is diagnosed with DCIS but also has heart disease and diabetes, the physician must balance the risks vs the benefits of treating this patient with surgery and radiation against the relatively slow progression of disease (perhaps over 10 years or longer) and the relatively low risk of invasive recurrence in the patient’s lifetime. On the other hand, treatment should perhaps be more aggressive for a woman diagnosed at age 40, but even then, biology of the tumor is likely to be an important determinant of risk for disease progression. A recent study showed that high-grade lesions, close margins of excision, and presentation with a palpable lesion all were associated with increased risk of recurrence. The same type of decision making can be applied to radiation therapy in women over age 70. Women with node-negative tumors that are ER-positive are likely to do well with...
either radiation therapy or tamoxifen alone for local control.\textsuperscript{107} In this group, the risk of death from breast cancer was in the 3% range after 4 years, whereas the likelihood of dying of other causes was >20%.\textsuperscript{106} However, tumors without hormone receptors, even in the elderly, are associated with higher local recurrence,\textsuperscript{108} suggesting again that understanding the underlying biology will help us to make better decisions in the future.

**Prevention**

Many of the cooperative group trials of hormonal therapy found that not only did tamoxifen decrease local and distant recurrence, but that it decreased the incidence of contralateral breast cancer as well. Several investigators initiated prevention trials with tamoxifen, the largest of which was NSABP P-01. The study population consisted of a large cohort of women (n = 13388) who were either ≥60 years, or 35 to 59 with a 5-year predicted risk for breast cancer >1.67 based on the Gail model.\textsuperscript{109} Women with lobular carcinoma in situ also were eligible for this study. The women were randomly assigned to receive either placebo or tamoxifen (20 mg/day) for 5 years (6694 women in each group).

The study found that tamoxifen reduced the risk of invasive breast cancer by 49%, with cumulative incidence at follow-up of 43.4 vs 22 per 1000 women in the placebo and tamoxifen groups, respectively, during 69 months. Risk also was reduced (56%) in women with a history of lobular carcinoma in situ and in those with any category of predicted 5-year risk. Women with a history of atypical hyperplasia had the greatest risk reduction (86%). Tamoxifen reduced the risk of noninvasive breast cancer by 50%. An additional benefit was a reduction in hip, radius, and spine fractures. However, increased risks for those taking tamoxifen included a higher rate of endometrial cancer and vascular events (ie, stroke, pulmonary embolism, and deep-vein thrombosis), predominantly in women older than age 60.\textsuperscript{106} The decision about whether to take tamoxifen for prevention requires a careful consideration of the actual risk of both developing and dying from breast cancer, in the context of the risk of other health threats. The development of tools that present information in a decision-ready context, so that risks and benefits can be weighed properly, will become increasingly important (Figures 4 and 5). Further progress will come from developing biomarkers to stratify risk and to specifically target interventions to a specific biomarker. Successful pairing of biomarkers that predict risk and benefit from therapy are likely to result in cost-effective prevention strategies.\textsuperscript{111}

The Institute of Medicine recently published a comprehensive report on ways to leverage biomarkers and emerging technology, as well as to better implement screening strategies to improve our ability to detect and prevent breast cancer.\textsuperscript{112}

**A Changing Paradigm—What the Future Holds**

Science and medicine have come a long way in just over a century since Halstead published his description of the radical mastectomy. Physicians and patients now may select from a myriad of treatment choices that include surgery (mastectomy vs lumpectomy), radiation therapy, chemotherapy, hormonal therapy, and other new alternative therapies. Innovations in the field of diagnostic imaging include digital mammography and high-resolution MRI scans, and positron emission tomography, which
may be coupled to specific biomarkers that will likely help predict response to therapy. Advances in surgical options and radiation therapy have reduced the pain and emotional trauma of the diagnosis of breast cancer for thousands of women and will continue to move the field into ever more targeted and individualized therapy.

Future directions for research include the development of genetic and phenotypic markers for the determination of risk to help determine which patients stand to benefit most from screening and aggressive treatment. We have already seen the introduction of one such test for node-negative women. Importantly, these tools also will be powerful predictors of response to radiation, hormonal intervention, and chemotherapy. In addition, clinical trials with correlative scientific studies will help to refine the current complex algorithm for the treatment of both DCIS and invasive cancer. Knowledge gained from these studies may help target future therapy toward preventing progression of disease, possibly obviating the need for surgical excision. In the future, molecular and imaging markers in combination with clinical parameters will help individually characterize breast cancer type, predict response to therapy, determine prognosis, and ultimately dictate the informed treatment choices women make in conjunction with their physicians.

**CONCLUSION**

Breast cancer is complex and represents a number of different diseases. The integration of molecular phenotyping in the context of clinical trials and outcomes is likely to reveal that specific tumor types are more associated with recurrence whereas others are likely to be much more benign. Some phenotypes are more or less responsive to chemotherapy than others. An enormous effort is under way to characterize tumor response and delineate the specific pathways that are abnormal in tumors that are less responsive to standard therapies, with the goal of better designing the introduction and testing of biologically targeted therapies. The next decade holds in store the unraveling of the tumor types and the appropriate tailoring of therapy to biology and patient preference.

**REFERENCES**


