Clinical Medicine Reviews in Womens Health

REVIEW

Current and Evolving Therapeutic Options in the Treatment of Early Breast Cancer

Gerald M. Higa

Schools of Pharmacy and Medicine and the Mary Babb Randolph Cancer Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA.

Abstract: Improvements in overall survival and patient quality of life highlight the remarkable progress in breast cancer over the past two decades. Even though these outcomes are frequently attributed to early diagnosis, new surgical techniques, novel agents, and a better understanding of the biology of the disease, the impressive achievements would not have occurred without patient participation in well-designed clinical trials. And while it is counter-intuitive to believe that the complexity of a disease can be made even more complicated by *results* of scientific research, this is likely to be true for breast cancer. Nevertheless, the conquest of the disease is being relentlessly pursued by cancer researchers who, like Cervantes' fictional character, are convinced that their quest against unseemly odds is not misguided fantasy.

Keywords: adjuvant therapy, aromatase inhibitors, chemoprevention, DCIS, early breast cancer, neo-adjuvant therapy, sentinel node, tamoxifen

Clinical Medicine Reviews in Womens Health 2011:3 1–21

doi: 10.4137/CMRWH.S1636

This article is available from http://www.la-press.com.

The Quest

Survival and well-being are, arguably, the single most important objective and subjective endpoints in oncology. If this is true, then decreased breast cancer mortality and improved survivor quality of life should be two of the more notable clinical achievements over the past 20 years. Moreover, this trend will probably continue into the next decade. While early detection and advances in local-regional and systemic therapies are frequently associated with the former achievements, the continued development and further refinement of gene-based risk-stratification templets will likely contribute to the latter prediction. However important the aforementioned interventions have been, or may be, the improved outcomes would not have occurred in the absence of conducting and completing well-designed clinical trials. The validity of this conclusion is supported by several pieces of evidence including: a) the physical and psychological implications of breast-conserving surgery; b) the reduction of morbidity associated with lymphatic mapping and sentinel node biopsy; c) the identification of tumor characteristics that aid selection and duration of targeted systemic therapies; and d) the validation of risk-recurrence tools based on gene expression patterns that specifies a subset of patients who can be spared from chemotherapy.

Although well appreciated, it is still important to emphasize that early breast cancer does not refer simply to primary operable tumors; rather the diagnosis is a conglomeration of heterogeneous diseases embedded with a vast array of unique tumor characteristics, molecular signatures, and behavioral patterns. This notion is further supported by the variable duration of long-term disease-free survival among the majority of these patients and the stark reality that as many one-third of those with "early" breast cancer will develop locally recurrent or metastatic disease. While the search for cause and cure is not uncommon for cancers in general, the *quest* in breast cancer has taken on Quixote-like features; undaunted by the countenance of a stealthy adversary, researchers and physicians continue to tilt the odds in favor of surviving the disease.

The impetus for undertaking this review is to prepare a referable document in which the contents would be informative and instructive. While compelling, the supporting evidence is also controversial. Nonetheless, the reader will gain an appreciation for the increased, though by no means complete, understanding of the disease and its management. As such, this paper highlights a number of landmark clinical trials that changed treatment standards, discusses areas where uncertainty still exists, and identifies critical research questions.

The Foe

Breast cancer is the most common malignancy diagnosed in American women and for reasons not completely understood the incidence of invasive disease has decreased slightly over the past 10 years.[1] In 2010, approximately 207,000 new cases are anticipated in American women alone. This statistic becomes even more striking when translated as six new diagnoses occurring every 15 minutes. Although the second leading cause of cancer-related deaths, breast cancer is not the most lethal malignant disease in women. Part of the explanation for this apparent contradiction relates to the observation that approximately 60% of the patients are diagnosed with disease that appears to be localized (early) to the primary site; another 30% present with tumor involving the regional nodes or extending beyond (locally advanced) the primary location.[2] These data figure prominently in the significant improvement in five-year survival rates from 75% to 89% ($P < 0.05$), during the mid-1970's and 1996–2004, respectively.

Early detection

One of the factors frequently linked to the improved outcomes relates to detection early in the natural history of the disease. This notion is supported by the finding that of the estimated 200,000 new breast cancers diagnosed annually in the United States (US), approximately 85%–90% of the patients have tumors amenable to surgery based on staging criteria alone.[2] Furthermore, detection of the vast majority of these cases, especially in those with tumors less than 1 cm, were aided primarily by mammography. While evidence indicates that screening mammograms can reduce breast cancer deaths, this survival benefit is greater in women 50 years of age and older compared to women in their fourth decade of life. Part of this discrepancy may be related to the lower age-related incidence; it is also possible that more aggressive disease observed in younger women contributes to the

poorer overall survival rate.[3] Nonetheless, reductions in mortality attributable to mammography have been estimated to range from 15% to 35%.[4]

The importance of these data notwithstanding, the US Preventive Task Force (USPTF) created a tempest in November 2009, when their recommendations regarding screening mammograms became public. Contrary to their 2002 statement which recommended mammography every 1 to 2 years for women aged 40 years and older, their current position advises against routine imaging studies in women under the age of 50 years. Tempering this position somewhat, the statement adds that the ultimate decision should consider an individual patient's perspective regarding potential benefits and risk of the screening program.[5] The apparent basis for the USPTF recommendation stems from the most recent Cochrane review in which Danish authors analyzed seven clinical trials involving approximately 600,000 asymptomatic women who were randomized to screening or no screening.[6] Although their findings indicated the likelihood that mammography reduces breast cancer deaths, the authors found that screening also resulted in overdiagnosis as well as over-treatment. Numerically, for every 2,000 women screened over a period of 10 years, only one had a survival benefit; however, 10 of the screened population were diagnosed with breast cancer and received treatment unnecessarily. Hence, these data, which not only highlight the uncertain magnitude of the beneficial effect but also propose that screening is implicitly harmful, may have been one of the major considerations for the current USPTF recommendation.

Two attempts to improve the sensitivity of mammography led to: 1) digitized imaging, which has the capability of visually enhancing the image by magnifying and applying contrast to suspicious areas of the breast and 2) MRI (magnetic resonance imaging). Although the overall accuracy is similar to regular mammography, the first technique shares many features associated with digital cameras including storage capability, portability, and accessibility. In addition, patients are exposed to less radiation.[7] Not unexpectedly, this new technology is more expensive than regular mammography.

The possible utility of MRI as a screening tool is based on the concept of using a small molecular magnetic agent (ie, gadolinium) that provides excellent contrast between various soft tissues in the breast including adipose, parenchymal, and cancerous lesions. Over the past 10 years, six studies have been conducted to determine the benefit of adding MRI to regular mammography for women deemed to be at increased risk of breast cancer (eligibility criteria included documented *BRCA1* or *BRCA2* mutation or strong family history; some of the studies even included women with a prior history of breast cancer).[8–13] The one consistent finding in all of the published studies was that MRI outperformed mammography in detecting invasive breast cancer in these high risk patients; sensitivity ranged between 70% to 95% and 30% to 40%, respectively. Even though more cancers were detected by MRI, the positive predictive value was less than 40%. In contrast, nearly all studies indicated that MRI was less specific than mammography, which resulted in additional imaging studies and biopsies being performed in up to 15% of patients. Clearly less than perfect, screening MRIs may lead to increased physical discomfort and psychological distress in participants and even their care givers.[10,14] And perhaps adding to the psychological stress, especially in women with very high disease-risk factors, access to centers with MRI expertise appears to be limited. Finally, results of a cost-utility analysis of screening MRIs in the United States have been published.[15] To estimate health and economic outcomes, a cohort of women between 25 to 69 years of age was incorporated into a Monte Carlo simulation model. Quality-adjusted life-year (QALY) was selected as a measure of health benefit. The cost per QALY gained with mammography only and mammography plus MRI ranged between $19,000–$29,000 and $43,000–$731,000, respectively. Intra-numerical difference was dependent on age; inter-numerical difference was related to specific *BRCA* mutation. Comparative costing among several ranges of age indicated that the most cost-effective strategy (of adding MRI to annual mammography) occurred in women aged 35 to 54 years who harbored a *BRCA1* mutation with a cost of approximately $55,000; the calculated figure for the same age range in patients with *BRCA2* mutations was nearly $131,000.

While the above data appear equivocal, guidelines for combining MRI with annual screening mammography were prepared by an expert panel based on their interpretation of available evidence.[16] As a result,

the consensus panel recommended the addition of MRI for women with either *BRCA* mutation or a first-degree relative of a (*BRCA*) mutation carrier. Other instances where addition of MRI appear to be appropriate (even in the absence of *BRCA* testing) include women less than 40 years old who have a lifetime risk of 20%–25% or greater and those who received therapeutic mantle irradiation (such as patients with Hodgkin's Disease) within the previous 30 years.

Local-regional therapy

Although controversy exists regarding the actual health outcome benefits of screening, early detection *is* associated with smaller tumors and, at least in part, an improved prognosis. An evolution in the understanding of breast cancer biology led to a number of groundbreaking clinical trials, the results of which had a significant impact on the surgical management of early disease.[17–19] Foremost, a striking paradigm reversal has occurred, one where optimal benefit could be achieved with minimal, rather than maximal, intervention. Long-term follow-up of patients who had breast-conserving surgery (BCS) provided strong evidence that disease-free and overall survival is similar regardless of the extent of the surgical procedure.[20,21] Even though more patients can be offered lumpectomy (plus radiation therapy), mastectomy may be performed depending on tumor and/or breast size, tumor location, presence of multifocal disease in the affected breast, and patient-related factors such as individual preference or a reluctance to receive (or contraindication to) radiation therapy. However, advances including skin-sparing and nipple-areola complex (NAC)-sparing procedures have even occurred with mastectomy, though neither are considered standard practice.[22,23] Whereas prospective studies have not been conducted, the ipsilateral recurrence rate following skin-sparing mastectomy has been reported to be less than 5%;[24] and reconstruction does not appear to interfere with detection of the local recurrence.[25] Furthermore, while NAC-sparing surgery is cosmetically and possibly functionally appealing, the physiological (and psychological) benefit must be balanced against the risk of tumor involvement, which on retrospective analysis has been found to be in the range of 5% to 10%.[26,27] Unfortunately, and despite the number of publications, none included patient quality of life as a study endpoint. And though speculative, breast reconstruction using the conserved skin could have a favorable effect on the woman's perception of body image and sexuality, more so if sensation of the NAC can be preserved.

Considering the importance of staging and prognostic information obtained from the regional nodes, the consequences of arbitrary sampling and complete axillary lymph node dissection (CALND) were in and of themselves also problematic; the former may miss and therefore understage the disease, the latter leads to substantial morbidity. Hence, both methods were subject to much controversy. Intuitively, a less aggressive yet more accurate surgical procedure would likely have a major impact in the overall management of breast cancer. The use of a gamma probe (technetium sulfur colloid) provided surgeons with the ability to identify the axillary lymphatics and localize the first (ie, sentinel) node.[28,29] Minimally invasive and with high predictive accuracy (believed related to the greater scrutiny of serially-sectioned tissue), sentinel node biopsy (SNB) has become the standard method to assess tumor invasion of the ipsilateral nodes. Equally important is the impact SNB has had on improving patient quality of life.

Even though axillary nodal status is a critical component of disease staging, it should be emphasized that only prognosis (not disease outcome) is altered for each stage by the new procedure. This conclusion appears to be supported by the *improved* survival among women whose nodal status was negative by SNB compared to those that had node-negative disease by routine histologic examination following partial or complete axillary dissection.[30] What is implied by this observation is that the better prognosis and survival benefit resulted, in part, from more accurate staging. An apparent contradiction to this belief was another report that resection of fewer nodes (0–10 vs. ≥20) was associated with a higher risk of dying from breast cancer.[31] Although possible explanations for this finding include understaged disease resulting from fewer nodes examined and/or a possible therapeutic role of CALND, one cannot discount the importance of sentinel lymph node mapping and subsequent removal of the sentinel node for pathologic examination. Hence, the difference may not be purely due to number of nodes examined.

Because of the changing patterns of diagnosis, prognosis, and treatment, a new staging system for breast

cancer was officially adopted in 2003. Although much more comprehensive, the increased details included in the 6th edition of the American Joint Committee on Cancer Staging Manual did not totally eliminate the likelihood of having disparate findings. For example, patients with small tumors (ie, pT1, ≤20 mm) and a sentinel node containing only minimal disease (ie, pN0[i+], ≤0.2 mm) have been reported to have poorer breast cancer-specific survival compared to those with pT1 tumors with no evidence (pN0[i–]) of nodal involvement.[32] This difference is notable in light of the fact that significantly more patients with pN0[i+] also received systemic adjuvant therapy. However, results of a large clinical trial are, at least in part, inconsistent with the previous finding.[33] While investigators of this study reported that the presence of micrometastasis in the sentinel node had no impact on overall survival, the presence of microscopic disease in the bone marrow was associated with an increased the risk of death. Further clouding the issue regarding the association between SNB and survival among women with small tumors is that the increased incidence of node-positive disease is not uniform for all T1 and T2 tumors.[34] Except for stage II, the authors of this report found that survival was not consistently altered though factors such as tumor grade, size of the sentinel node tumor deposit, and the presence of remaining axillary-positive nodes could have impacted their results. The latter consideration may be particularly relevant in patients with N0[i+] and N1mi (ie, >0.2 mm but ≤2 mm) disease. Retrospective evaluation of nodal tissue from both subgroups of patients who chose to undergo CALND indicated tumor involving *non-sentinel* nodes in 15.5% and 9.3% of the patients, respectively.[35] These percentages are limited by the fact that only information from patients with positive sentinel nodes who underwent CALND was used to arrive at their conclusion. Nonetheless, compared to patients with no evidence of microscopic nodal disease (ie, N0[i–]), disease-free and overall survivals were much shorter among women with N1 mi disease; no survival differences were observed between women with N0(i+) and women with N0(i–) nodes with one notable exception, that overall survival among N0[i+] patients who had CALND was significantly better those who did not.

Updated results of another large clinical trial indicate that regional control, disease-free survival, and overall survival in patients with clinically *node-negative* early breast does not appear to be significantly different regardless if CALND is added to SNB compared to SNB alone.[36] This finding also implies that CALND would not likely confer any additional survival benefit if *only* the sentinel node was involved. The simplicity of this suggestion, however, is complicated by the daunting challenge of determining the status (in a non-invasive way) of distal nodes in patients with sentinel node-positive disease.[37–39]

Although not without debate, the collective data imply that sentinel node-positivity is of prognostic and clinical relevance;[40,41] so is the role of CALND in patients with non-sentinel node involvement. Because of the correlation between size of metastasis and incidence of non-sentinel node involvement, CALND appears to be justified in cases of ≥2 mm tumor deposits in the sentinel node.[42,44,45] However, justification for routine axillary-clearing dissection is not as clear in patients with deposits ≥0.2 mm but ≤2 mm despite reports of survival disadvantage in cases with even occult metastasis.[37]

Adjuvant chemotherapy

Results of numerous clinical trials demonstrated superior outcomes when a taxane was added to an anthracycline-containing regimen.[46–48] Two frequently used regimens for patients with node-positive or high-risk node-negative disease include four cycles of either docetaxel or paclitaxel following four cycles of doxorubicin plus cyclophosphamide (ie, sequential AC-Taxane).[49] Another is the combination of docetaxel and cyclophosphamide (TC) for four cycles.[50,51] Although these three regimens are the closest to what may be considered "standard therapy", this status is not without uncertainty or controversy. While there have been no head-to-head clinical trials comparing either of the AC-Taxane and TC regimens, it has been suggested that the 24 week sequential AC-T (docetaxel) is superior to the 12 week TC regimen because one of the arms in NSABP (B-30) trial included 12 weeks of A plus TC (ie, concurrent ATC). However, this conclusion may not be valid for a number of reasons. First, approximately one year after the B-30 trial was opened to enrollment, the doses of concurrent ATC had to be modified because of five treatment-related deaths in this arm. As such, the dosages of the TC and ATC regimens were not identical. Thus, the

superior outcomes observed with the sequential AC-T regimen may be due, in part, to increased dose intensity and/or cumulative dose of the drugs in the respective regimens rather than purely a longer duration of treatment. It is also notable that the improved tumor outcomes achieved with sequential AC-T, though statistically superior, were still quite modest. Second, while longer duration of therapy (ie, sequential AC-T) had a significant impact on DFS and overall survival, there could have been subsets of patients that did not achieve any further benefit even by having treatment prolonged from 12 weeks to 24 weeks. It is even conceivable that this subgroup of patients would have similar outcomes (and therefore preferable) with the shorter duration TC regimen. Third, in this relatively large randomized clinical trial it could be anticipated that 10%–20% of the tumors would be HER2-positive. Hence, a number of different combinations of [tumor] biologic features (ie, node-positive, ER (estrogen receptor)-positive, HER-negative; node-positive, ER-negative, HER-positive; node-positive, ER-negative, HER-negative; etc.) could have also affected survival outcomes both dependent (predictive) and independent (prognostic) of treatment regimen.[52–55]

Finally, it is important to note that approximately 15% of all breast cancers do not express ER, PR, and HER2 (ie, triple-negative). While lacking predictive markers for hormonal and HER2 therapies, this particular breast cancer phenotype appear to be sensitive to pharmacologic strategies targeting VEGF (vascular endothelial growth factor),[56] the microtubule,[57] and the PARP(poly [adenosine diphosphate-ribose] polymerase) 1 enzyme.[58] With regards to the latter, preliminary data in patients with advanced triple-negative breast cancer indicate that the addition of a PARP 1 inhibitor to DNA-damaging agents such as the platinum compounds is more effective than chemotherapy alone.[58] Analysis of approximately two-thirds on the 123 enrolled patients showed significant improvement in clinical benefit rate ($P = 0.0012$), progression-free survival ($P = 0.0003$) and overall survival ($P = 0.0012$) among those randomized to receive the PARP inhibitor. Notable also was the similarity of adverse events in both groups. Although premature, these data suggest that targeted inhibition of PARP may be useful in the adjuvant setting for patients with triple-negative breast cancer.

Chemotherapy in the elderly

Even though most, if not all, breast cancers can be included into one of four major subgroups (based on expression of hormone and HER2 receptors), the overall percentage in each group appears to differ by menopausal status. For example, the more favorable biological tumor characteristics including the presence of hormone receptors and absence of HER2 (ie, ER+/PR (progesterone receptor)+, HER2-negative) is the most frequently observed subtype (ie, luminal A subtype) in postmenopausal women.[59] Coupled with these receptor characteristics, breast cancer in the elderly is also likely to exhibit other molecular features (ie, low Ki-67 expression, normal *p53*) associated with less aggressive tumor behavior.[60] While these findings suggest that adjuvant chemotherapy is less frequently indicated in older women with early breast cancer, the lower usage [of chemotherapy] is also partly due to patient age and as well as the attendant concerns of drug-induced toxicity. In addition, relatively fewer older patients, especially over 65 years of age, have been enrolled clinical trials designed to assess the benefits of chemotherapy. Thus, except for younger postmenopausal women with hormone receptor-negative, node-positive tumors and few co-morbid health problems, the benefits of chemotherapy in the elderly may be vastly underappreciated.[61] Nonetheless, breast cancers that should be treated with chemotherapy include the HER2-enriched and the basal-like subtypes. In addition, chemotherapy should be *considered* for some patients with luminal A (ER+, node-negative or node-positive) and luminal B (low hormone receptor, high Ki-67 expression) tumors with high risk-recurrence scores (ie, RS $\geq$31, OncotypeDx) as well as those with ER+/HER2-overexpresseing tumors.

While these intrinsic tumor subtypes help identify subsets of patients who are most likely to benefit from chemotherapy, it is equally important to evaluate the functional status (ie, presence of co-morbidities) and psychological well-being of the patient.[62] Support for evaluation of the former can be found in two retrospective studies which showed an association between patients with greater numbers of co-morbid conditions (such as cardiovascular and respiratory disorders, diabetes, kidney or liver disease, and smoking) and higher breast cancer- and non-breast cancer-related

mortality rates.[63] Implied in this finding also is the axiom that the relatively poorer prognosis associated with hormone receptor-negative disease is likely to be worsened by chemotherapy-induced toxicities. Even though both notions are valid, the second fails to balance the risk against possible benefits. As such, many older patients may be undertreated simply by default. Results of a recently published randomized clinical trial provide some perspective regarding this important issue.[64] The study was designed to test the non-inferiority of single agent capecitabine against two frequently used chemotherapy regimens (AC and CMF, cyclophosphamide + methotrexate + fluorouracil) in patients ≥65 years of age; patients with hormone receptor-positive tumors received endocrine therapy following completion of chemotherapy. Of the 633 patients enrolled, 307 were randomized to capecitabine, 326 to multi-agent chemotherapy. Of the latter group, 133 and 184 patients received CMF and AC, respectively. At the first prescribed analysis (when 600 patients were enrolled), 24 recurrences, distant metastases, or death from any cause had occurred in the capecitabine group compared to a total of 16 events in the chemotherapy group. Although small in terms of number of events, the predictive probability still suggested that longer term follow-up would demonstrate capecitabine to be inferior. Approximately one month later, the trial was closed to further enrollment. After a median of 2.4 years (maximum of 5.6 years) of follow-up, relapses and deaths (due to breast cancer) were two-fold higher among patients treated with capecitabine. Notably, the most significant survival benefits occurred in patients with hormone receptor-negative tumors; relapse-free survival and overall survival were more than three times higher among those receiving the multi-agent regimens. As expected, the incidence of toxicity was greater with the two- and three-drug regimens, especially hematologic-related events; hand-foot syndrome was the most frequently reported adverse event in patients receiving capecitabine. Two drug-related deaths occurred, both in the capecitabine arm. Interestingly, the highest and lowest number of patients completing their planned treatment involved the multi-agent regimens, AC (92%) and CMF (62%); 80% completed the planned capecitabine therapy. These data suggest that standard agents should be considered for patients, regardless of age, in who adjuvant chemotherapy is indicated. The use of the TC (docetaxel plus cyclophosphamide) regimen is a reasonable alternative to AC when potential cardiac toxicity is a major concern.

Adjuvant endocrine therapy

The presence of estrogen and progesterone receptors has been the most useful predictor of response to hormonal therapy. Generally considered a favorable prognostic feature, hormone receptors are found relatively more frequently in postmenopausal (than premenopausal) breast cancers.

Postmenopausal women

Collectively, small, node-negative, hormone-responsive breast cancer is associated with a reasonably good prognosis, made even better by estrogen-deprivation therapy. Such survival benefits are summarized in a large meta-analysis of adjuvant tamoxifen in patients with ER-positive tumors.[65] Despite the drug's efficacy, not all patients respond to tamoxifen and at least half of all relapses and deaths occur after completing five years of hormonal therapy. Nonetheless, when compared to surgical and other pharmacologic strategies, part of tamoxifen's success was due to an improved tolerability profile. Hence, it is somewhat ironic that a major stimulus for developing new hormonal agents was related to adverse events associated with tamoxifen therapy. Because the final step in converting androgens to estrogens is catalyzed by aromatase, a new generation of aromatase inhibitors (AIs) was developed to block the synthesis of estrogens. Based on superior outcomes in postmenopausal women with hormone receptor-positive metastatic breast cancer,[66–68] a number of clinical trials were conducted comparing one of the AIs against tamoxifen as adjuvant therapy for postmenopausal women who had completed local treatment and were eligible to receive adjuvant hormonal therapy. The earliest study evaluated safety and efficacy outcomes of anastrozole versus tamoxifen, or the combination of both agents (ie, ATAC).[69] More than 9000 postmenopausal women with early breast cancer who completed primary therapy and were eligible to receive adjuvant endocrine therapy were randomized to one of three treatment arms containing nearly equal numbers of patients. Eighty-four percent of the enrolled patients (7,839) had confirmed hormone-receptor-positive tumors. Planned for five years of treatment, the first analysis

of data was performed after a median follow-up of approximately 3 years. Most of the major endpoints favored anastrozole alone compared to tamoxifen: the risk of relapse was 17% lower (HR, 0.83; 95% CI 0.71–0.96; $P = 0.013$); development of contralateral breast cancer was lower (HR, 0.42; 95% CI 0.22–0.79; $P = 0.007$) as well as a lower incidence of endometrial carcinoma ($P = 0.02$), clotting and cerebrovascular events ($P = 0.0006$ for both), vaginal bleeding and hot flashes ($P < 0.0001$ for both). The only (safety) outcome which was significantly better with tamoxifen involved the musculoskeletal system. Notably, the finding that combined therapy was not superior to tamoxifen alone led to the closure of that arm of the study.

When outcomes data were analyzed after a median follow-up of 8.3 years, a number of endpoints including [longer] DFS ($P = 0.003$), [delayed] time-to-recurrence ($P = 0.0001$), [reduced] distant metastases ($P = 0.022$, and [lower incidence of] contra-lateral breast cancer ($P = 0.004$) were significantly improved with anastrozole.[70] These data suggest the carryover effect (after 5 years of treatment) is significantly greater with adjuvant anastrozole.

While the clinical benefits are tempered somewhat by bone fractures, which occurred more frequently among patients receiving anastrozole ($P < 0.0001$) during the period of active treatment, the difference was not significant thereafter. Even though no difference in overall survival has been observed after a median of more than seven years, a survival benefit appears to be emerging with *sequential* administration of anastrozole (as well as the other AIs) after 2 to 5 years of initial tamoxifen therapy.[71–73]

Results of adjuvant trials comparing letrozole or exemestane against tamoxifen demonstrate similar between-group differences favoring the AIs.[74,75] Data accumulated over the past 10 years suggest that all three AIs are equally effective in improving DFS; the only advantage anastrozole may have is financial as it has only recently become available as a generic drug.

The compelling clinical evidence has led to the recommendation of incorporating an AI as part of the hormonal therapy for most, if not all, postmenopausal women with hormone receptor-positive early breast cancer. Although the selection of the AI will likely reside with the physician, the decision regarding initiating therapy with an AI or tamoxifen may ultimately be made by the patient based on side effect profiles associated with each type of estrogen-deprivation therapy. Nevertheless, the selected AI can be given initially for five years, or following 2–5 years of tamoxifen therapy for an additional five years.

Premenopausal women

Because of the concern that the inhibitory effect of the AIs on estrogen synthesis could be reversed in women with functioning ovaries,[76] tamoxifen (for 5 years) is the only absolute endocrine intervention recommended for pre- and peri-menopausal women with hormone receptor-positive breast cancer (outside of a clinical trial). Despite the unquestionable clinical benefits and the purported anti-tumor carryover effect, a small but significant number of patients experience disease relapse (even during therapy or) after tamoxifen is stopped. Although poorer outcomes had initially been reported with longer (than 5 years) durations of the anti-estrogen,[77] two large clinical trials are currently being conducted to assess the clinical benefits of extended tamoxifen therapy (up to 10 years).[78,79] A combined total of approximately 24,000 patients have been enrolled in the ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) and aTTom (adjuvant Treatment Tamoxifen Offers More) trials (Table 1); neither study has been prematurely discontinued because of a negative impact on DFS with continued tamoxifen therapy. The optimal duration of tamoxifen is, therefore, still unknown.

In the absence of chemotherapy, no apparent benefits have been observed with combined estrogen deprivation using an LHRH (luteinizing hormone-releasing hormone) agonist and tamoxifen;[80] the same, however, may not be true with surgical ablation added to tamoxifen.[65] This unexpected inconsistency is supported by data indicating that ovariectomy plus tamoxifen have a favorable impact on both DFS and OS in patients with ER-positive tumors.[81] Interestingly, patients in this study had tumors that also overexpressed HER2. One other clinically relevant issue is the therapeutic role of chemotherapy-induced ovarian suppression/ablation.[82,83] While it is intuitive to believe that younger women with ER-positive breast cancers would benefit most from this outcome, a statistically significant improvement in disease-free and overall survival, regardless of hormone receptor status and therapy, has been reported in premenopausal women

Table 1. Selected clinical trials in progress

Design	Eligibility	Treatment schema
ATLAS (Adjuvant Tamoxifen, Longer Against Shorter) Randomized trial of 10 versus 5 years of adjuvant tamoxifen	Premenopausal women who completed 5 years of adjuvant tamoxifen	5 additional years of tamoxifen vs. observation
aTTom (adjuvant Tamoxifen—To offer more?) Randomized trial of 10 versus 5 years of adjuvant tamoxifen	Women with ER+ or ER-unknown invasive breast cancer	5 additional years of tamoxifen vs. observation
ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) Study Phase III randomised, open label, four-arm study comparing lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab as adjuvant therapy following at least four cycles of anthracycline or non-anthracyline chemotherapy in patients with HER2- overexpressing and/or amplified breast cancer.	Age ≥ 18 yrs Performance status (ECOG) ≤ 1 Non-metastatic, unilateral, ≤T3, non-inflammatory, primary operable, invasive adenocarcinoma of the breast	Trastuzumab × 1 yr vs. lapatinib × 1 yr vs. trastuzumab (12 or 18 weeks, by assigned design) followed by a six-week treatment-free interval followed by lapatinib (28 or 34 weeks, by assigned design) vs. trastuzumab in combination with lapatinib for 1 yr Patients enrolled according to one of two design schemas, with Design 2 having two chemotherapy options (Design 2 and 2B), and will be randomised to one of four treatment regimens within each design schema.
SOFT (Suppression of Ovarian Function Trial) Phase III, randomised, multicentre study of the role of ovarian function suppression (OFS) in combination with either exemestane or tamoxifen compared to tamoxifen alone as adjuvant therapies for pre-menopausal women with endocrine-responsive breast cancer.	Targeted enrollment of 3,000 premenopausal patients	Ovarian suppression + exemestane (×5 yrs) vs. Ovarian suppression + tamoxifen (×5 yrs) vs. Tamoxifen alone (×5 yrs) Note: Suppression of ovarian function to be achieved by either LHRH agonist, surgical- or radiation-induced ablation
TEXT (Tamoxifen and Exemestane Trial, IBCSG 25-02) Phase III randomized trial comparing OFS plus either tamoxifen or exemestane.		OFS (with triptorelin) from the start of adjuvant therapy followed by 5 yrs of tamoxifen or exemestane. Chemotherapy, if given, should be started with the triptorelin.

Endpoints	Preliminary data	Author comment
1°—disease recurrence and OS 2°—cause-specific deaths; second primary cancers; and of major events requiring hospitalisation.	12% reduction in the risk of breast cancer recurrence in extended arm (HR, 0.88, $P = 0.005$).	Accrual completed March 2005; follow-up phase. Hormone receptor status in ~40% of patients not known.
1°—disease recurrence and OS 2°—cause-specific deaths; second primary cancers	At a median follow-up of 4.2 years, fewer recurrences among those allocated to 10 yrs tamoxifen (415 vs. 442; RR = 0.94, 95% CI 0.81–1.09; $P = 0.4$).	Accrual completed March 2005; follow-up phase. Hormone receptor status in 61% of patients not known.

(*Continued*)

Table 1. (*Continued*)

Design	Eligibility	Treatment schema
	Breast cancer mortality lower among those allocated 10 yrs, though data are immature. Although the risk of endometrial cancer doubled with 10 yrs tamoxifen, there was no increase in deaths from endometrial cancer or from any other non-breast cancer cause.	Further follow-up required to assess effects on recurrence and mortality.
1°—DFS 2°—OS, TTR, TTDR, safety and tolerability, incidence of brain metastasis. Analyses conducted separately for cohorts of patients defined by presence or absence of cMyc oncogene amplification, expression level of PTEN and presence or absence of the p95HER2 receptor.		Data are awaited.
1°—DFS 2°—OS, QOL, and side effects secondary to induction of early menopause		Data are awaited as it may help define the optimal adjuvant endocrine therapy of premenopausal breast cancer.
1°—DFS 2°—OS, QOL		Data are awaited as it may help define the optimal adjuvant endocrine therapy of premenopausal breast cancer

who developed (chemotherapy-induced) amenorrhea that lasted at least six months.[49] Whether this finding is truly causal rather than merely correlative remain uncertain.

Adjuvant HER2 therapy

The knowledge that endocrine therapy alone can improve survival in patients with early, hormone-responsive breast cancers also embraces the concept that specific treatment depends, in part, on identification of unique tumor characteristics. Hence, the ability to probe the disease at the molecular level led to the discovery of a novel oncogene that encodes the HER2 protein.[84] Since the pivotal report which showed that targeting HER2 with trastuzumab resulted in demonstrable survival benefits in patients with metastatic disease,[85] numerous clinical trials have been conducted in patients with HER2-overexpressing, early breast cancer.[86–88] The consistent findings among all of the trials regarding survival benefits regardless of nodal status, timing of administration, and chemotherapy (ie, anthracycline- or non-anthracycline-containing) regimens, led to a new treatment standard for patients with HER2-positive early breast cancer. Thus, the sequential addition of docetaxel (T) and trastuzumab (H) following doxorubicin plus cyclophosphamide (AC-TH) should be strongly considered for HER2-overexpressing early-stage breast cancer, especially in patients at low risk for cardiovascular morbidity (Table 2). An alternative regimen that may be used is concurrent administration of docetaxel, carboplatin, and trastuzumab (TCH).

Because of the demonstrated activity of lapatinib, a dual HER1/HER2 kinase inhibitor, a complex four-arm phase III study (known as ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) comparing lapatinib and trastuzumab either alone, in combination or in sequence as adjuvant therapy of ErbB2 overexpressing and/or amplified breast cancer is currently enrolling patients (Table 1).

Table 2. Selected adjuvant therapy regimens.

Intrinsic subtype	RS	Premenopausal	Postmenopausal	Comment
Luminal A	<18	Tamoxifen 10 mg BID × 5 yrs	Anastrozole 1 mg QD or Letrozole 2.5 mg QD Both AIs are recommended either as 1st-line therapy for 5 years. If tamoxifen given initially for 2–3 years, follow with anastrozole or exemestane 25 mg to complete 5 years. If tamoxifen given initially for 4–5 years, follow with letrozole for 5 more years.	Await results of ATLAS and aTTom clinical trials
Luminal A	18–30	Tamoxifen 10 mg BID × 5 years +/– chemotherapy AC-T (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q 21 days × 4 cycles; then docetaxel 100 mg/m^2 Q 21 days × 4 cycles)	AI (as above) and if chemotherapy eligible consider anthracyline- or taxane-containing regimen	The use of anthracylines and taxanes in elderly patients is associated with improved 10-year survival rates but greater toxicities.
Luminal A	≥31	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q 21 days × 4 cycles; then docetaxel 100 mg/m^2 Q 21 days × 4 cycles followed by tamoxifen 10 mg BID × 5 years	If chemotherapy eligible as above followed by an AI × 5 years	The greatest benefit generally occurs in those with the highest risk for recurrence, the fewest co-morbid health problems, and longest life expectancy
Luminal B		Consider chemotherapy (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q 21 days × 4 cycles; then docetaxel 100 mg/m^2 Q 21 days × 4 cycles) followed by tamoxifen 10 mg BID x 5 years	If chemotherapy eligible consider anthracyline- or taxane-containing regimen followed by an AI × 5 years	As indicated above
HER2-positive		(AC-TH), doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 Q 21 days × 4 cycles followed by paclitaxel 175 mg/m^2 Q 21 days × 4 cycles (or paclitaxel 80 mg/m^2 Q week × 12 weeks) + trastuzumab 4 mg/kg loading dose, then 2 mg/kg^2 Q weekly total of 52 weeks or AC followed by docetaxel 100 mg/m^2 Q 21 days × 4 cycles + trastuzumab 4 mg/kg loading dose, then 2 mg/kg^2 Q weekly total of 52 weeks or TCH (docetaxel 75 mg/m^2 + carboplatin AUC 6) Q 21 days × 6 cycles + concurrent trastuzumab 4 mg/kg loading dose, then 2 mg/kg Q weekly × 52 weeks	If chemotherapy eligible consider AC-TH or TCH	As indicated above
Triple-negative		AC-paclitaxel or docetaxel Q 21 days × 4 cycles	If chemotherapy eligible consider AC-T or TC	Await results of PARP-1 and mitotic spindle inhibitors

Neo-adjuvant therapy

In contrast to strong evidence supporting the use of *adjuvant* chemotherapy, endocrine therapy, and more recently, trastuzumab, results of clinical trials published over the past 10 years do not indicate a *survival* advantage when systemic therapy is given *prior* to surgery in patients with large though operable, non-inflammatory breast cancer.[89–91] Nonetheless, preoperative administration of chemotherapy is considered standard of care for locally advanced, stage IIIB and some stage IIIA tumors; much fewer data have been published regarding the use of agents targeting the estrogen and HER2 receptors.[92–94] Part of the rationale for the use of neo-adjuvant therapy relates to the similar overall survival outcomes regardless of extent of the surgical procedures.[95] While not minimizing the relevance of increasing the rate of breast-conserving therapy, it is somewhat unfortunate that this appears to be the only proven benefit of neo-adjuvant therapy.

As in the adjuvant setting, an anthracycline, a taxane, and cyclophosphamide should form the backbone of neo-adjuvant chemotherapy regimens. Treatment usually consists of four cycles of AC or up to six cycles of TAC. An eight cycle regimen, which consists of four cycles of AC followed by four cycles of docetaxel has also been reported to be effective.[91,96] In this latter study, the pathological complete response rate (pCR) was nearly doubled with sequential use of docetaxel (AC-T) given preoperatively compared to AC (26.1% and 13.7%, $P < 0.001$). Despite the higher pCR rate, the difference in DFS rates (HR = 0.92; 95% CI, 0.78 to 1.08; $P = 0.29$) and OS rate (~75% in all groups; $P = 0.76$) at 8.5 years of follow-up is not significant.[97] However, among those who did achieve a pCR (compared to those who did not), this endpoint is correlated with significantly improved DFS (HR = 0.49, $P < 0.0001$) and OS (HR = 0.36, $P < 0.0001$) rates. Others have reported the same association.[98] The major caveat is that most patients appear to derive very little benefit even with addition of the taxane. Still, these findings suggest that more patients are able to have BCS without adversely affecting DFS or OS.[99,100]

Preoperative (neo-adjuvant) systemic therapy provides the clinician with a unique opportunity to assess real-time tumor response, an appraisal that cannot be performed during the course of adjuvant therapy. However, clinical response (ie, based on physical or radiographic examination) does not always correlate with pathologic response (residual disease found on histologic examination). Furthermore, the criteria for or definition of a pCR needs to be standardized. Whereas the definition used by the NSABP is no evidence of malignant cells in the breast, MD Anderson Cancer Center includes the axillary nodes as well.[97,101]

The use of neo-adjuvant *endocrine* therapy alone would be a desirable option in view of three important findings. First, the lower response rates achieved with chemotherapy in patients with hormone receptor-positive (compared to receptor-negative) tumors; second, the disproportionately higher incidence of early, receptor-positive breast cancer in postmenopausal women; and third, the demonstrated efficacy of the aromatase inhibitors (AI). Two phase III trials have been conducted comparing an AI to tamoxifen.[102,103] Although not large by breast cancer clinical trial standards, the Letrozole P024 study provides the strongest evidence of the superiority of an AI as sole neo-adjuvant therapy for postmenopausal women who were not candidates for BCS at the time of diagnosis. In double-blind fashion, 154 patients were randomized to receive letrozole (2.5 mg daily) for four months; 170 women were treated with tamoxifen (20 mg daily) for the same duration. The superiority of letrozole was observed in all study endpoints including clinical response rate (CR+PR, 55% vs. 36%; $P < 0.001$) as well as numbers of patients who underwent BCS (45% vs. 35%; $P = 0.022$). Interestingly, the response rate in those whose tumors overexpressed HER2 was also significantly higher in the letrozole arm (88% vs. 21%); $P = 0.0004$).

Although another phase III study did not demonstrate any difference among all major endpoints, there were a number of issues that could have influenced the negative outcomes. Compared to the P024 study, the IMPACT trial included fewer numbers of patients in each treatment group, smaller tumors (some of which were amenable to BCS at diagnosis), 10-fold lower expression of ERs, and shorter duration (ie, 3 months) of hormonal therapy.

Neo-adjuvant endocrine therapy with an AI (ie, letrozole) alone is a reasonable option for early, hormone-dependent breast cancer in postmenopausal patients who would desire BCS and who are not likely be treated with chemotherapy. However, this should not be a routine option in otherwise healthy, younger women.

A distinct clinico-pathologic disease is an entity known as inflammatory breast cancer. The appearance of spongy dermal edema and erythema plus the absence of a palpable breast mass has been mistaken for an infectious process. Truly inoperable disease at the time of diagnosis, objective responses can be achieved in up to 80% of patients treated with neo-adjuvant chemotherapy, most of who will then become candidates for surgical resection.[104] Combined modality post-surgical treatment has resulted in a dramatic improvement in five-year survival compared to those who do not receive any form of systemic therapy.

Because patients with locally advanced breast cancer have benefited from neo-adjuvant therapy, the therapeutic strategy has also been applied to patients with early (ie, stage I or II) breast cancer. Although the number of patients who could have BCS (and who would not otherwise been candidates for such a procedure) was increased, pre-surgical systemic therapy with doxorubicin and cyclophosphamide did not improve DFS and OS.[90] However, subset analysis of patients who achieved a pCR indicates significantly lower risk of disease recurrence and possibly improved long-term survival outcomes.

That attaining a pCR appears to be an important predictor of survival suggests that patients with HER2-positive, locally-advanced breast cancer could also benefit from pre-operative systemic therapy with trastuzumab. Over the past four years, several groups have reported significantly higher pCRs in small numbers of patients who received trastuzumab as part of the treatment regimen.[104,105] These early findings were supported by results from a large phase III clinical trial that were presented recently.[106] Compared to chemotherapy alone, patients who received chemotherapy plus trastuzumab had significantly higher pCR rates (20% vs. 39%; $P = 0.002$) and event-free survival rates, 53% vs. 70% (HR, 0.56; $P = 0.006$). Furthermore, in contrast to one of the early studies,[105] the improved outcomes in this trial was observed in patients regardless of concomitant ER status. Although not currently approved for use in this setting, it is likely that trastuzumab will receive FDA approval as part of neo-adjuvant therapy in the near future.

DCIS

Not invasive by definition, DCIS (ductal carcinoma *in-situ*) has been excluded from the number of breast cancer diagnoses. However, if included, DCIS would increase the statistic by approximately 20%. Notably, the sharpest increase in incidence occurs during the fourth decade of life. Even though most breast cancers are diagnosed after menopause, this should not necessarily imply that DCIS is a precursor lesion to invasive disease. In fact, the prognosis is excellent as more than 95% of patients with DCIS have long-term, disease-free survival with currently available therapies. Nonetheless, DCIS remains a conundrum. For example, although not *invasive*, approximately 5% of patients have sentinel node involvement at diagnosis. However, the significance of microscopic nodal involvement is still not known. Moreover, other than the presence of hormone receptors (which is in and of itself also quite variable), there is a paucity of other molecular markers that provide sufficient prognostic information. Furthermore, while the disease is usually indolent, high-grade DCIS found in some patients is strongly associated with either tumor recurrence or progression to invasive breast cancer.

Considered *early* and *limited*, most DCIS is treated with BCS, radiation, and tamoxifen (regardless of hormone receptor expression).[90] The addition of tamoxifen was based on results following 7-years of follow-up showing that the addition of tamoxifen significantly improved DFS rates.[107] This improvement was primarily attributable to a reduction in the incidence of events in both ipsilateral and contralateral breasts. Notably, tamoxifen reduced the rate of all *invasive* breast cancer events by 45% ($P = 0.0009$); the reduction of non-invasive breast cancer events by tamoxifen was not significant. Furthermore, the effect of tamoxifen in reducing ipsilateral breast cancer was irrespective of age, margin status, or presence/absence of comedo necrosis.

These results notwithstanding, the NSABP B-24 study evaluated the extent to which tamoxifen benefits correlated with hormone receptor expression.[108] Of the total number of tumors with information available related to receptor status, 77% were ER-positive. Among tamoxifen-treated patients, the risk of a breast cancer event was decreased by 59%, $P = 0.0002$; the relative risk of an event occurring in patients with ER-negative tumors was not significantly reduced. However, because of the relatively smaller numbers in the receptor-negative group, a meaningful clinical benefit could not be definitely ruled out. These

results are indeed consistent with previous findings in patients with invasive breast cancer treated with adjuvant tamoxifen. Estrogen receptor status should be routinely assessed in patients with DCIS to determine whether adjuvant tamoxifen should be included in the overall management program.

Prevention

While the improved survival rates are noteworthy, two other statistics add another perspective to the disease. First, less than 10% of all patients diagnosed with breast cancer have metastatic disease at the time of presentation; and second, approximately one-third of the patients with early-stage disease eventually relapse.[65] Thus, these two groups will account for the majority of patients who will ultimately succumb to the disease.

Conceivably, mortality from breast cancer will be even lower if the disease could be prevented or were altogether less common. One strategy that can reduce the risk of developing the disease, especially in women with *BRCA1* and *BRCA2* mutations is surgery.[109,110] Although risk reduction can be achieved with prophylactic bilateral mastectomy, some patients have still developed breast cancer after the surgical procedure. Thus, while substantial the reduction in risk is not absolute.[111,112] Three clinical studies, each based on the association between estrogens and breast cancer, have demonstrated that chemoprevention can reduce the risk of developing invasive breast cancer in patients at high-risk for the disease.[90,113,114] Despite these historic findings, the response to using tamoxifen or raloxifene has been tepid, often bordering on indifference. The lack of a uniform buy-in is frequently attributed to concerns about the toxicities of treatment. Tethered to this concern is the fact that large numbers of otherwise healthy women would need to be treated in order to reduce the incidence of a relatively small absolute number of cancers. Because the issue of routine prophylaxis for high-risk women is largely dependent on benefits and risks of treatment, it is reasonable to re-consider the important aspects of chemoprevention. First, a comparative trial between tamoxifen and raloxifene in *postmenopausal* women has shown that while breast cancer risk reduction is comparable, therapy with raloxifene is not associated with an increased risk of endometrial cancer.[114] It is also important to note that development of this second malignancy does not appear to be increased (and may even be less) in *premenopausal* women treated with tamoxifen.[115,116] Second, only tamoxifen has been shown to reduce the risk of breast cancer in premenopausal women. Third, while most toxicities of tamoxifen occur during the period of treatment, the carry-over effect of risk-reduction benefits extends far beyond the treatment period.[117] In essence, the therapeutic index improves substantially with time. Fourth, early retrospective analysis of *CYP2D6* polymorphisms provided exciting information regarding identification of high-risk patients who would most likely benefit from tamoxifen.[118–120] However, conflicting results of a recent genomic study have led to confusion regarding a particular subset of patients who should not be treated with tamoxifen.[121] Hence, routine evaluation of *CYP2D6* polymorphisms is currently not recommended.

Quality of life

Even though careful assessment of tumor characteristics has been instrumental in the management of the disease, it is clear that cure has not been achieved in all patients with early breast cancer. Equally important, though perhaps less appreciated, is the psychological toll the disease exacts on the patient.

While society is much more conscious about breast cancer diagnoses today, this was not the case 30 years ago. Our current culture would likely be unnerved by the chilling reality that prior to 1980 most patients with the disease were never told their diagnosis because of the emotional response it would evoke.[122] Although women with breast cancer now have the opportunity to be intimately involved in treatment decisions, they have also espoused a need for ensuring that their psychosocial well-being is cared for as well. Commonplace fears, once fueled by the mutilating surgery and its subsequent assault on femininity and sexuality, are still present and manifested in similar ways.[123,124] In addition to the broad range of affective disorders associated with the diagnosis and surgery, cognitive deficits experienced by patients may also be caused by chemotherapy and hormonal therapy.[125]

As breast cancer survival continues to improve it is conceivable that many patients with early disease will not die of the malignancy but rather heart-and diabetes-related complications which claim the lives of approximately 435,000 American women annually.[126]

Considering the already high prevalence (ie, estimated 50 million Americans) of metabolic syndrome and its association with cardiovascular disease and type 2 diabetes, it is concerning that some breast cancer treatment, especially estrogen-deprivation strategies, can affect quality of life by increasing the risk of developing this potentially morbid syndrome.[127–130]

One additional component of the management of patients with breast cancer that impacts both physical and psychosocial outcomes is supportive care. While advances in supportive care are, at least, partly responsible for improving both types of outcomes, more efficacious anti-tumor strategies may also be accompanied by additional stressors and burdens in terms of side effects and duration of therapy. A prime example relates to women with early, hormone receptor-positive breast cancer who are likely to receive adjuvant endocrine therapy for up to 10 years, of which three to eight years may be with an aromatase inhibitor (AI). The negative impact of AIs on bone mineralization, however, may be prevented or attenuated by adjunctive bisphosphonate therapy.[131] More intriguing were the results from a clinical trial that adding a bisphosphonate to endocrine therapy significantly prolonged disease-free and relapse-free survival compared to endocrine therapy alone.[132] While provocative, these findings do not change the current standard of care as the results must be confirmed by a larger clinical trial.

The Inquest

A number of issues need to be resolved or at least further clarified. First, the proposed change in guidelines regarding screening mammography. While the timing of the announcement by the USPTF suggests that the current recommendations were influenced, at least in small part, by a very fragile economy and an eye on reforming the delivery of health care, it is also be somewhat counterintuitive because late diagnoses in a subset of younger women are likely to result in higher overall treatment costs as well as a greater risk of dying from the disease. Second, the current practice of performing a CALND in patients who have a positive sentinel node is supported by the greater accuracy of SNB, the belief that (even) micrometastasis is clinically relevant, and the observation that axillary dissection contributes to improvement in survival. Nonetheless, the divergent results of published studies also suggest that CALND may be safely avoided in a subgroup of cases. The credibility of this conclusion may be linked to contemporary tumor characteristics, method of detection, and gene expression profiles. The latter is especially noteworthy because of its role in predicting prognosis as well as identifying a subgroup of patients unlikely to benefit from adjuvant chemotherapy (more of which is discussed below). Third, uncertainty still persists with regards to whether ovarian suppression plus tamoxifen or an AI (in addition to chemotherapy) is more effective in premenopausal patients without occurrence of amenorrhea. The results of two phase III trials (SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial) currently in progress are expected to provide answers to this therapeutic dilemma which will further optimize adjuvant endocrine therapy for hormone receptor-positive breast cancer (Table 1). As clinical trials attempt to clarify the role of castration in premenopausal women with hormone-dependent breast cancer, it is equally important that these studies also assess the overall impact inducing menopause has on the physical, psychological, and emotional well-being of these patients. Fourth, a lesson learned from hormonal therapy of breast cancer that needs to be applied to HER2-positive disease is the incorporation of genomics in treatment decisions. Just as there is a subset of patients with ER-positive breast cancer who do not appear to benefit from addition of chemotherapy (to hormonal therapy), there may be an analogous subgroup of patients with ER- and HER2-positive tumors who may benefit from therapies targeting each receptor alone. Discovery of such genomic and/or proteomic profiles will reduce the incidence and severity of toxicities associated with the addition of chemotherapy. Furthermore and in contrast to hormonal therapy, no subset of patients who benefits from trastuzumab therapy alone has been identified. However, this notion may not be absolutely valid because most of the clinical trials did not enroll patients with node-negative, HER2-positive tumors measuring <1 cm. Indeed, retrospective data indicate that patients with HER-2 positive T1a (>0.1 but ≤ 0.5 cm) and T1b (>0.5 cm ≤ 1 cm) tumors in their greatest dimension who were treated with surgery +/– radiation only had a significantly higher risk of recurrence than patients with HER2-negative disease.[133,134] These data suggest that the subgroup of patients with very small

HER2-positive tumors may benefit from adjuvant therapy targeting the receptor alone. Fifth, the coupling of standard of care with many uncertainties appears to be somewhat paradoxical. Yet, this is applicable to adjuvant trastuzumab. While the improved survival outcomes appear to hinge on administering adjuvant trastuzumab for one year, similar benefits may result with much shorter durations of therapy.[88] Hence, 12 months may not be the optimal duration of therapy. In addition, outcomes data suggest that the combination of docetaxel (T), carboplatin (C) and trastuzumab (H) may be a reasonable alternative to standard anthracycline-based regimens.[135] The latter consideration is based on most recent results of the BCIRG 006 study which indicated significant improvements in DFS and OS with TCH and AC-TH compared to AC-T. Notable also, the small numerical DFS advantage observed in the AC-TH arm was achieved with greater toxicity in almost all parameters measured; a higher incidence of congestive heart failure and acute leukemia diagnoses occurring only in patients receiving AC as part of their treatment. While these data suggest that anthracycline-based regimens may not be truly superior, the other numerical reality is that more patients in the TCH arm die of breast cancer than heart disease and leukemia. Because the absolute (though small) survival benefits must be balanced against the (relatively low) incidence of cardiac and neoplastic disease, the patient should be informed of the alternatives and involved in making the decision. Sixth, the higher risk of developing CNS disease as the first site of recurrence among patients receiving trastuzumab suggests that a small molecule inhibitor of the HER2 kinase may be more effective in the adjuvant setting.[87,136] This issue is one of the secondary objectives of the ALTTO clinical trial (ClinicalTrials.gov Identifier: NCT00490139). Seventh, the demonstrated efficacy of the third-generation AIs suggests that this class of agents may be potentially better than tamoxifen as adjuvant therapy for DCIS. The completion of NSABP B-35 comparing anastrozole and tamoxifen as adjuvant therapy for five years plus radiation following lumpectomy in postmenopausal women with DCIS will provide comparative outcome measures related to DFS, OS, and especially, quality of life (QOL). It will be equally imperative to follow these patients long after adjuvant hormonal therapy is completed.

The Dream

The concept of targeted therapy may have originated with the treatment of hormone-responsive breast cancer but other malignant diseases such as chronic myelogenous leukemia, multiple myeloma, and carcinomas of the kidney, colon, and even lung provide the substantial evidence for its continued evolution. Success, however, has not been absolute. For example, although endocrine therapy is the treatment of choice for hormone receptor-positive breast cancer, as many as 40% of ER-positive tumors does not respond to estrogen deprivation. The same can be said for targeted treatment of HER2-positive breast tumors. Furthermore, and though highly specific, these agents often are not necessarily tumor selective as evidenced by their side effect profiles.

The future clear lies in tailored individualized therapy. Arguably, the most significant advance in the management of early breast cancer over the last decade has been the application of genomics to determine the risk of disease recurrence.[137] Grouped by Oncotype DX recurrence scores (RS), three subgroups of patients with hormone receptor-positive, node-negative breast cancer have emerged; a low-risk group (RS <18) who can be treated with oral endocrine therapy alone and a high-risk group (RS ≥ 31) who achieved significant benefit from addition of chemotherapy.[138] Treatment of the third group (intermediate risk, RS 18–30) has been more challenging as the benefits of adding chemotherapy is not pronounced. A large clinical trial (known as TAILORx) currently in progress has been specifically designed to address this issue. While this study may provide additional insight regarding the value of chemotherapy in this subgroup, it is conceivable that the process of refining risk recurrence scores can be improved by combining the RS with pathological (P) and clinical (C) characteristics. Preliminary results that this may indeed be possible were reported recently.[139] By means of a retrospective meta-analysis, the investigators assessed risk of distant recurrence at 10 years using both RS and pre-selected P (ie, tumor size and grade) and C (ie, patient age) features. The combined RSPC risk index resulted in significantly fewer patients being classified as intermediate-risk compared to the RS alone (18% vs. 26%; $P = 0.001$), respectively. Hence, it may be possible in the near future to further enhance individual treatment decisions.

Table 3. Summation standards.

1. Screening mammography should begin at age 40. If the USPTF recommendations are followed, women should be informed of screening's risk/benefit when begun at a later age.
2. CALND is currently supported by the greater accuracy of SNB, the biological and clinical relevance of microscopic disease, and the association with improved survival.
3. Sequential AC-Taxane improves tumor outcomes but may not be necessary for all patients in who chemotherapy is indicated.
4. The use of anthracylines and taxanes in elderly patients is associated with improved 10-year survival rates but more toxicity. The greatest benefit generally occurs in those with the highest risk for recurrence, the fewest co-morbid health problems, and longest life expectancy.
5. AIs should be used in most, if not all, postmenopausal women with hormone receptor-positive early breast cancer. The selected AI can be given initially for 5 years, or following 2–5 years of tamoxifen for an additional 5 years.
6. Tamoxifen should be used in all premenopausal women with ER-positive breast cancer including those with adverse prognosis subtypes.
7. Endocrine therapy (ie, AIs and tamoxifen) should follow completion of chemotherapy even though the evidence to support this practice is not absolutely conclusive.[65,140] However, the increased incidence of embolic events observed with concurrent chemohormonal therapy especially in postmenopausal patients makes the sequential approach preferable.[141]
8. Ovarian ablation/suppression (OAS) does not appear to confer additional benefit to tamoxifen (with or without chemotherapy) except in women who do not experience amenorrhea. Further evidence of the importance of chemotherapy-induced ovarian suppression is the associated improvement in survival regardless of hormone receptor status.
9. Trastuzumab should be part of the treatment of patients with HER2-overexpressing tumors. Until further data emerge, the duration of trastuzumab therapy is one year.
10. Neo-adjuvant chemotherapy should utilize the same agents that are used in the adjuvant setting. Addition of trastuzumab to chemotherapy should be given in a clinical trial. Neo-adjuvant letrozole should be considered as the endocrine therapy of choice in postmenopausal women with ER-positive tumors who are not candidates for chemotherapy.
11. Treatment of DCIS includes BCS, radiation, and tamoxifen (regardless of hormone receptor expression). Of note, BCS plus radiation is associated with a higher risk of local (disease) recurrence compared to mastectomy, 12% vs. 1%, respectively.
12. Chemoprevention for breast cancer is available and should be reconsidered.
13. Long-term effects of hormonal therapy should be considered as long term survival increases.
14. Genomics and proteomics will enable further customization of tailored therapy.

Even though the full impact of genomics on breast cancer has not been realized, it is conceivable that proteomics could provide an even better (tailored) fit between patient, tumor and treatment. This notion is supported by the fact that one gene can produce multiple versions of a specific protein. In addition, compared to the relatively stable genome, proteins are altered constantly in response to internal and external stimuli. As such, unique proteins may be associated with risk of cancer development, detection of early disease, response to, and adverse effects of, therapy, as well as early recurrence and overall prognosis. Harnessing the potential of proteomics will be a daunting challenge, perhaps none more so than tumor-associated proteins. While identification of selective candidate proteins can provide a glimpse, recognition of incriminating protein patterns or signatures will further delineate the foe.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010 Jul 7. [Epub ahead of print] doi:10.3322/caac.20073.
2. Surveillance Epidemiology and End Results. SEER Stat Fact Sheets: Breast Cancer. SEER Cancer Statistics Review 1975–2005. http://seer.cancer.gov/statfacts/html/breast.html. Accessed July 23, 2010.
3. Brinton LA, Sherman ME, Carreon JD, Anderson WF. Recent trends in breast cancer among younger women in the United States. *J Natl Cancer Inst*. 2008;100:1643–8.
4. Autier P, Hery C, Haukka J, Boniol M, Byrnes G. Advanced breast cancer and breast cancer mortality in randomized controlled trials on mammography screening. *J Clin Oncol*. 2009;27:5919–23.

5. US Preventive Services Task Force. Screening for breast cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2009;151:716–26.
6. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database of Systematic Reviews*. 2009;4: Art. No. CD001877. doi:10.1002/14651858.CD001877. pub3.
7. Dershaw DD. Film or digital mammographic screening? *N Engl J Med*. 2005;353:1846–7.
8. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004;351:427–37.
9. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol*. 2005;23:8469–76.
10. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet*. 2005;365:1769–78.
11. Lehman CD, Blume JD, Weatherall P, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer*. 2005;103:1898–905.
12. Sardanelli F, Podo F. Breast MR imaging in women at high risk of breast cancer. Is something changing in early breast cancer detection? *Eur Radiol*. 2007;17(4):873–87.
13. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 2004;292:1317–1325.
14. Van Dooren S, Seynaeve C, Rijnsburger AJ, et al. Exploring the course of psychological distress around two successive control visits in women at hereditary risk of breast cancer. *Eur J Cancer*. 2005;41:1416–25.
15. Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA*. 2006;295:2374–84.
16. Saslow D, Boetes C, Burke W, et al. American Cancer Society Guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57:75–89.
17. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med*. 1985;312:674–81.
18. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Re-analysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1995;333:1456–61.
19. Veronesi U, Salvadori B, Luini A, et al. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. *Eur J Cancer*. 1995;31A:1574–9.
20. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–41.
21. Veronesi U, Cascinelli N, Mariani MD, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347: 1227–32.
22. Slavin SA, Schnitt SJ, Duda RB, et al. Skin-sparing mastectomy and immediate reconstruction: oncologic risks and aesthetic results in patients with early-stage breast cancer. *Plast Reconstr Surg*. 1998;102(1):49–62.
23. Sacchini V, Pinotti JA, Barros AC, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg*. 2006;203:704–14.
24. Carlson GW, Bostwick J, Styblo TM, et al. Skin-sparing mastectomy: oncologic and reconstructive considerations. *Ann Surg*. 1997;225:570–8.
25. Slavin S, Love S, Goldwyn R. Recurrent breast cancer following immediate reconstruction with myocutaneous flaps. *Plast Reconstr Surg*. 1994;93: 1191–204.
26. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple-areola complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol.* 1999;6:609–13.
27. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Ann Surg Oncol*. 2002;9:165–8.
28. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol*. 1993;2:335–9.
29. Guiliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg*. 1994;220:391–8.
30. Langer I, Guller U, Hsu-Schmitz SF, et al. Sentinel lymph node biopsy is associated with improved survival compared to level I and II axillary lymph node dissection in node negative breast cancer patients. *Eur J Surg Oncol*. 2009;35(8):805–13.
31. Polednak AP. Survival of lymph node negative breast cancer patients in relation to the number of lymph nodes examined. *Ann Surg*. 2003;237:163–7.
32. Leidenius MH, Vironen JH, Heikkila PS, Joensuu H. Influence of isolated tumor cells in sentinel nodes on outcome in small, node-negative ($pT_1 N_0M_0$) breast cancer. *Ann Surg Oncol*. 2010;17:254–62.
33. Cote R, Giuliano AE, Hawes D, et al. ACOSOG Z0010: a multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2N0M0 breast cancer (abstract). *J Clin Oncol*. 2010;28(18S):958s.
34. Vanderveen KA, Schneider PD, Khatri VP, Goodnight JE, Bold RJ. Upstaging and improved survival of early breast cancer patients after implementation of sentinel node biopsy for axillary staging. *Ann Surg Oncol*. 2006;13:1450–6.
35. Cox CE, Kiluk JV, Riker AI, et al. Significance of sentinel lymph node micrometastases in human breast cancer. *J Am Coll Surg*. 2008;206: 261–168.
36. Krag DN, Anderson SJ, Julian TB, et al. Primary outcome results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (NSR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients (abstract LBA505). *J Clin Oncol*. 2010;28(18S):948s.
37. Houvenaeghel G, Nos C, Mignotte H, et al. Micrometastases in sentinel lymph node in a multcentric study: predictive factors of non-sentinel lymph node involvement. *J Clin Oncol*. 2006;24:1814–22.
38. Van Zee KJ, Manasseh DM, Bevilacqua JL, et al. A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol*. 2003;10:1140–51.
39. Specht MC, Kattan MW, Gonen M, Fey J, van Zee KJ. Predicting nonsentinel node status after positive sentinel lymph biopsy for breast cancer: clinicians versus nomogram. *Ann Surg Oncol*. 2005;12:654–9.
40. Dowlatshahi K, Fan M, Snider HC, Habib FA. Lymph node micrometastases from breast carcinoma: reviewing the dilemma. *Cancer*. 1997;80:1188–97.
41. Noguchi M. Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes. *Br J Surg*. 2002;89:1505–15.
42. McCready DR, Yong WS, Ng AK, Miller N, Done S, Youngson B. Influence of the new AJCC breast cancer staging system on sentinel lymph node positivity and false-negative rates. *J Natl Cancer Inst*. 2004;96:873–5.
43. Zavagno G, Luca de Salvo G, Bozza F, et al. Number of metastatic sentinel nodes as predictor of axillary involvement in patients with breast cancer. *Breast Cancer Res Treat*. 2004;86(2):171–9.
44. Dabbs DJ, Fung M, Landsittel D, McManus K, Johnson R. Sentinel lymph node micrometastasis as a predictor of axillary tumor burden. *Breast J*. 2004;10(2):101–5.
45. Marin C, Mathelin C, Neuville A, et al. Sentinel lymph node biopsy with micrometastases in breast cancer: histological data and surgical implications. *Bull Cancer*. 2003;90:459–65.
46. Hugh J, Hanson J, Cheang MC, et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. *J Clin Oncol*. 2009;27:1168–76.
47. Henderson IC, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol*. 2003;21:976–83.

48. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol*. 2005;23:3686–96.
49. Swain SM, Jeong J-H, Geyer CE, et al. Longer therapy, iatrogenic amenorrhea, and survival in early breast cancer. *N Engl J Med*. 2010;362:2053–65.
50. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol*. 2006;24:5381–7.
51. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol*. 2009;27:1177–83.
52. Hayes DF, Thor AD, Dressler LG, et al. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med*. 2007;357:1496–506.
53. Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. *N Engl J Med*. 1994;330:1260–6.
54. Ross JS, Fletcher JA. The HER-2/*neu* oncogene in breast cancer: prognostic factor, predictive factor, and target for therapy. *Oncologist*. 1998;3:237–52.
55. Donegan WL. Tumor-related prognostic factors for breast cancer. *CA Cancer J Clin*. 1997;47:28–51.
56. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357:2666–76.
57. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol*. 2007;25:5210–7.
58. O'Shaughnessy J, Osborne C, Pippen J, et al. Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP 1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patient with metastatic triple-negative breast cancer (TNBC): results of a randomized phase II trial (abstract 3). *J Clin Oncol*. 2009;27 (Suppl 18S):793S.
59. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst*. 2000;92:550–6.
60. Eppenberger-Castori S, Moore DH Jr, Thor AD, et al. Age-associated biomarker profiles of human breast cancer. *Int J Biochem Cell Biol*. 2002;34: 1318–30.
61. Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *J Clin Oncol*. 2006;24:2750–6.
62. Taylor WC, Muss HB. Adjuvant chemotherapy of breast cancer in the older patient. *Oncology (Williston Park)*. 2010;24:608–13.
63. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *JAMA*. 2001;285:885–92.
64. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med*. 2009;360:2055–65.
65. Early Breast Cancer Trialists' Collaborative Groupt (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet*. 2005;365:1687–717.
66. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol*. 2000;18:3758–67.
67. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol*. 2003;21:2101–9.
68. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26:4883–90.
69. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomized trial. *Lancet*. 2002;359:2131–9.
70. Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group, Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC Trial. *Lancet Oncol*. 2008;9:45–53.
71. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet*. 2005;366:455–62.
72. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004;350:1081–92.
73. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361:766–76.
74. The Breast International Group (BIG) I-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353:2747–57.
75. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years tamoxifen treatment (Intergroup Exemestane Study): a randomized controlled trial. *Lancet*. 2007;369:559–70.
76. Wander HE, Blossey HC, Nagel GA. Aminoglutethimide in the treatment of premenopausal patients with metastatic breast cancer. *Eur J Clin Oncol*. 1986;22:1371–4.
77. Fisher B, Dignam, J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst*. 2001;93:684–90.
78. Peto R, Davies C. ATLAS (Adjuvant Tamoxifen, Longer Against Shorter): international randomized trial of 10 versus 5 years of adjuvant tamoxifen among 11,500 women—preliminary results. The ATLAS Collaboration (abstract). *Breast Cancer Res Treat*. 2007;106:48.
79. Gray RG, Rea DW, Handley K, et al. aTTom (adjuvant Tamoxifen—To offer more?): randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6, 934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—preliminary results (abstract). *J Clin Oncol*. 2008;26(15S):10s.
80. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet*. 2007;369:1711–23.
81. Love RR, Duc NB, Havighurst TC, et al. HER-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer. *J Clin Oncol*. 2003;21:453–7.
82. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol*. 2005;23:5973–82.
83. Vanhuyse M, Fournier C, Bonneterre J. Chemotherapy-induced amenorrhea: influence on disease-free survival and overall survival in receptor-positive premenopausal early breast cancer patients. *Ann Oncol*. 2005;16:1283–8.
84. Schechter AL, Stern DF, Vadyanathan L, et al. The neu oncogene: an erbB-related gene encoding a 185,000-Mr tumour antigen. *Nature*. 1984;312: 513–6.
85. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783–92.
86. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673–84.
87. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659–72.
88. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809–20.

89. Van der Hage J, van de Velde C, Julien J-P, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary breast cancer: results from the European Organization for Research and Treatment of Cancer Trial 10902. *J Clin Oncol*. 2001;19:4224–37.
90. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*. 1998;16:2672–85.
91. Bear HD, Anderson S, Brown A, et al. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol*. 2003;21:4165–74.
92. Hoff PM, Valero V, Buzdar AU, et al. Combined modality treatment of locally advanced breast carcinoma in elderly patients or patients with severe comorbid conditions using tamoxifen as the primary therapy. *Cancer*. 2000;88:2054–60.
93. Burstein HJ, Harris LN, Gleman R, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2- overexpressing stage II or III breast cancer: a pilot study. *J Clin Oncol*. 2003;21:46–53.
94. Arnould L, Arveux P, Couturier J, et al. Pathological complete response to trastuzumab-based neoadjuvant therapy is related to the level of HER-2 amplification. *Clin Cancer Res*. 2007;13:6404–9.
95. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomised clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1989;320:822–8.
96. Von Minckwitz G, Kümmel S, Vogel P, et al. Intensified neoadjuvant chemotherapy in early-responding breast cancer: phase III randomized GeparTrio Study. *J Natl Cancer Inst*. 2008;100:552–62.
97. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26:778–85.
98. Chollet P, Amat S, Cure H, et al. Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. *Br J Cancer*. 2002;86:1041–6.
99. Chen AM, Beric-Bernstam F, Hunt KK, et al. Breast conservation after neoadjuvant chemotherapy: the MD Anderson Cancer Center experience. *J Clin Oncol*. 2004;22:2303–12.
100. Boughey JC, Peintinger F, Meric-Bernstam F, et al. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. *Ann Surg*. 2006;244:464–70.
101. Hennessy BT, Hortobagyi GN, Rouzier R, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. *J Clin Oncol*. 2005;23:9304–11.
102. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol*. 2001;12:1527–32.
103. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double blind randomized trial. *J Clin Oncol*. 2005;23:5108–16.
104. Coudert BP, Arnould L, Moreau L, et al. Pre-operative systemic (neo-adjuvant) therapy with trastuzumab and docetaxel for HER2-overexpressing stage II or III breast cancer: results of a multicenter phase II trial. *Ann Oncol*. 2006;17:409–14.
105. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol*. 2005;23:3676–85.
106. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: primary efficacy analysis of the NOAH trial (abstract 31). *Cancer Res*. 2009;69.
107. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet*. 1999;353:1993–2000.
108. Allred DC, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: findings from NSABP Protocol B-24 (abstract 30). *Breast Cancer Res Treat*. 2002;76 (Suppl 1).
109. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol*. 2008;26:1331–7.
110. Friebel TM, Domchek SM, Neuhausen SL, et al. Bilateral prophylactic oophorectomy and bilateral prophylactic mastectomy in a prospective cohort of unaffected BRCA1 and BRCA2 mutation carriers. *Clin Breast Cancer*. 2007;7:875–82.
111. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst*. 2001;93:1633–7.
112. Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med*. 2001;345:159–64.
113. Vogel GV, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs. raloxifene on the risk of developing invasive breast cancer and other disease outcomes: NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2727–41.
114. Cuzick J, Forbes J, Edwards R, et al. First results from the International Breast Cancer Intervention Study (IBIS-1): a randomised prevention trial. *Lancet*. 2002;360:817–24.
115. Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med*. 2003;18:937–947.
116. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 2005;97:1652–62.
117. Cuzick J, Forbes J, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer—96 month follow-up of the randomised IBIS-I study. *J Natl Cancer Inst*. 2007;99:272–82.
118. Lim H-S, Lee HJ, Lee KS, Lee ES, Jang I-J, Ro J. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. *J Clin Oncol*. 2007;25:3837–45.
119. Bonanni B, Macis D, Maisonneuve P, et al. Polymorphism in the CYP2D6 tamoxifen-metabolizing gene influences clinical effect but not hot flashes. Data from the Italian tamoxifen trial. *J Clin Oncol*. 2006;24:3709–9.
120. Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol*. 2005;23:9312–8.
121. Dezentje VO, van Schaik RH, Vletter-Bogaartz JM, et al. Pharmacogenetics of tamoxifen in relation to disease-free survival in a Dutch cohort of the tamoxifen exemestane adjuvant multinational (TEAM) trial (abstract 508). *J Clin Oncol*. 2010;28(15S):70s.
122. Meyerowitz BE. Psychosocial correlates of breast cancer and its treatments. *Psychol Bull*. 1980;87:108–31.
123. Van Gestel YR, Voogd AC, Vingerhoets AJ, et al. A comparison of quality of life, disease impact and risk perception in women with invasive breast cancer and ductal carcinoma in situ. *Eur J Cancer*. 2007;43:549–56.
124. Rakovitch E, Franssen E, Kim J, et al. A comparison of risk perception and psychological morbidity in women with ductal carcinoma in situ and early invasive breast cancer. *Breast Cancer Res Treat*. 2003;77:285–93.
125. Abraham J, Haut MW, Moran MT, Filburn S, Lemiuex S, Kuwabara H. Adjuvant chemotherapy for breast cancer: effects on cerebral white matter seen in diffusion tensor imaging. *Clin Breast Cancer*. 2008;8:88–91.
126. Center for Disease Control and Prevention, National Vital Statistics System: LCWK10: Deaths, Percent of Total Deaths and Rank Order for 113 Selected Causes of Death, by Race and Sex: United States, 2001–06. Available at http://www.cdc.gov/nchs/nvss/mortality/lcwk10.htm. Accessed September 1, 2010.

127. Cuppone F, Bria E, Verma S, et al. Do adjuvant aromatase inhibitors increase the cardiovascular risk in postmenopausal women with early breast cancer? Meta-analysis of randomized trials. *Cancer*. 2008;112:260–7.
128. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353:2747–57.
129. Nguyen MC, Stewart RB, Banerji MA, Gordon DH, Kral JG. Relationships between tamoxifen use, liver fat and body fat distribution in women with breast cancer. *Int J Obes Relat Metab Disord*. 2001;25:296–8.
130. Dorum A, Tonstad S, Liavaag AH, Michelsen TM, Hildrum B, Dahl AA. Bilateral oophorectomy before 50 years of age is significantly associated with the metabolic syndrome and Framingham risk score: a control, population-based study (HUNT-2). *Gynecol Oncol*. 2008;109:377–83.
131. Hershman DL, McMahon DJ, Crew KD, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol*. 2008;26:4739–45.
132. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009;360:679–91.
133. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol*. 2009;27:5700–6.
134. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol*. 2009;27:5693–9.
135. Slamon DJ, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin, and trastuzumab (TCH) in HER2-positive early breast cancer patients: BCIRG 006 Study (abstract 62). *Cancer Res*. 2009:69.
136. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer (abstract). *J Clin Oncol*. 2007;25:512.
137. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351: 2817–26.
138. Paik S, Tang, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726–34.
139. Tang G, Cuzick J, Wale C, et al. Recurrence risk of node-negative and ER-positive early-stage breast cancer patients by combining recurrence score, pathological, and clinical information: a meta-analysis approach (abstract 509). *J Clin Oncol*. 2010;28(15S):70s.
140. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374:2055–63.
141. Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. *J Clin Oncol*. 1996;14:2731–7.