Survival Impact of Integrative Cancer Care in Advanced Metastatic Breast Cancer

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Abstract: Integrative cancer treatment is of substantial interest to many cancer patients. Research is needed to evaluate the effects of integrative treatment on patient outcomes. We report survival data for a consecutive case series of advanced metastatic breast cancer patients who received a comprehensive clinical program combining conventional treatments with nutrition and supplementation, fitness and mind-spirit instruction at the Block Center for Integrative Cancer Treatment. Treatment outcomes using integrative care for this disease have not previously been documented; survival data will thus contribute to decisions concerning future research directions and design. Ninety consecutive patients with metastatic breast cancer diagnosed during 1984–1997 who received chemotherapy at the integrative cancer center were included. Prognostic factors, treatments and survival from onset of metastases were determined from analysis of scans, labs, pathology and medical records. The log-rank test and Cox proportional hazards analyses were used, and a Kaplan–Meier curve was calculated. All patients had metastatic disease at baseline, 96% were relapsed and 52% had received prior chemotherapy for metastatic disease. Median age at onset of metastasis was 46 years. Median survival was 38 months (95% CI 27, 48). Published literature on populations with somewhat more favorable prognostic factors treated in conventional clinics showed median survivals of 20 to 23 months. Through the 1990s, median survival reported in metastatic breast cancer trials or observations generally ranged from 12 to 24 months. Five-year survival was 27% for Center versus 17% for comparison patients. Despite a higher proportion of younger and relapsed patients, survival of metastatic breast cancer patients at the Center was approximately double that of comparison populations and possibly even higher compared to trials published during this period. Explanations for the advantage relative to conventional treatment alone may include the nutritional, nutraceutical, exercise and psychosocial interventions, individually or in combination; self-selection of patients cannot be ruled out. Further research to evaluate the impact of integrative breast cancer treatment on survival is warranted.

Key Words: breast cancer, chemotherapy, integrative medicine, metastatic, nutrition

Despite therapeutic advances in recent years, the effectiveness of conventional treatment for metastatic breast cancer (MBC) is limited (1). A review of 189 randomized trials of chemotherapeutic and hormonal treatments for MBC published between 1975 and 1996 found only minimal survival differences among treatments: the most marked difference, found in comparisons of polychemotherapy versus monotherapy, yielded an absolute differential of only 3% 3 years after treatment (2). Through the 1990s, median survival in MBC ranged from 12 to 24 months (3); later trials of taxane-based therapies generally reported overall survivals of 18–26 months (4), with further improvements noted with the advent of
HER2-targeted antibody therapy (5). Nevertheless, these therapies introduce side effects and improve median survival by only a few months.

Breast cancer patients use complementary and alternative therapies in higher numbers than the population at large (6). Cancer patients who use alternative therapies in lieu of conventional interventions without professional guidance may have diminished survival (7), perhaps reflecting in part a population with high risk disease not responsive to conventional medicine. In contrast, the approach examined in the present study is a comprehensive integrative program guided by clinical assessments and selected biomarkers, combined systematically with conventional treatments by a physician-led team. In addition to widely recognized prognostic factors such as tumor size, ER status and lymph node invasion, other factors can impact survival in breast cancer patients, e.g. body weight, psychosocial distress with elevated catecholamines, cortisol, inflammatory and oxidative mediators, diet and physical activity (8). Randomized trials of single agent therapies or one-dimensional interventions appear inadequate to address this complexity, and the need for new clinical models to research and test whole systems interventions such as integrative care is becoming evident (9). Observations of characteristics and outcomes of integrative cancer treatment systems are suggested as a necessary first step in developing whole systems research models (10).

To date, reports on treatment outcomes for MBC patients using integrative cancer care in the United States are lacking. We report the outcomes and prognostic variables for 90 consecutive MBC patients attending a community-based facility near Chicago, the Block Center for Integrative Cancer Treatment (BCICT). The Block Center selectively integrates conventional cancer therapies with individualized nutritional biotherapy, nutraceutical support, fitness and physical care programs, and mind-spirit strategies. A major aim of this study is to supply preliminary observations on prognostic and outcome variables for integrative cancer treatment that can be used to determine future research directions and contribute to the design of future research.

**METHODS**

**Treatment**

The BCICT emphasizes a life-affirming, hope-based orientation in cancer treatment (11,12). Conventional, experimental, off-label and integrative treatments are provided, grounded in clinical and literature-based assessment of safety, efficacy and mode of action. For each of the integrative therapies (nutrition, physical care, mind-spirit care), specific laboratory and clinical assessments are performed to determine personal, clinical and biological needs of the patient, and to tailor treatment recommendations. Chemotherapy protocols are determined by the Center’s medical staff, following an initial detailed clinical workup, and are based on current medical literature, as well as prior treatment regimens.

Staff physicians with expertise in cancer nutrition develop a personalized nutrition and supplement regimen; utilizing this program, a registered dietitian then educates patients and provides hands-on training (13,14). Nutritional assessments include anthropometrics, individual caloric needs for weight gain or loss, and markers of nutritional, oxidative, immune, inflammatory status. The diet emphasizes intake of whole grains, fruits and vegetables with low glycemic indices, and proteins from plants, fish, dairy alternatives and egg whites. Supplements comprise a selected group of agents for which pre-clinical and clinical data have suggested a potential to mitigate side effects, enhance response to therapy, decrease resistance to chemotherapy and prolong disease remissions. Supplements taken by all patients in the study included fish oil, a multivitamin-mineral supplement designed for cancer patients, a mushroom-based immune supplement and a phytochemically-rich vegetable and fruit drink; other supplements frequently used include mixed carotenoids, melatonin, calcium-d-glucarate, reishi mushrooms and green tea. Supplement regimens are determined by favorable synergisms and screened for unfavorable interactions with conventional medications, and are recommended on the basis of individualized biochemical and molecular testing as well as treatment-related clinical assessments (e.g., side effects, disease complications, enhancing conventional treatment). In addition, patients receive intravenous vitamin infusions during chemotherapy to prevent treatment-related nutrient deficiencies. These infusions include vitamins A, C, D, E, K, B-vitamins and, at the time the study patients were treated, calcium, magnesium and trace minerals, all in doses slightly under to a few times higher than Recommended Daily Allowances. Our review of randomized trials of antioxidants (such as vitamins A, C,
and E) given with chemotherapy found no suggestion of negative impact on treatment response or survival, and potential improvements in chemotherapy side effects (15).

Each patient receives a physical care assessment including variables such as strength, endurance, range of motion, body composition analysis and exercise contraindications. Physical therapists or trainers instruct patients in the BCICT’s fitness program, which aims to improve aerobic competence and energy balance with interval and endurance training, to maintain or rebuild muscle mass with strength training, and to promote flexibility with therapeutic adaptations of yoga, Pilates and qi gong (16,17). Manual therapeutic techniques including microcurrent electrical stimulation, shiatsu, massage and acupuncture are implemented for pain management, chemotherapy-related side effects and improved well-being.

Each patient receives assessment and psycho-social education with staff psychotherapists in the BCICT’s mind-spirit program. Assessments utilize validated instruments and include mental health history, anxiety, depression and quality of life. Systematic training is provided in relaxation strategies, cognitive-behavioral interventions, and other approaches to enhance coping skills, pain management and sleep hygiene in order to manage the challenges associated with a cancer diagnosis and to mitigate side effects of chemotherapy, while improving treatment tolerance (18). Attending to issues of psychological well-being, lifestyle preferences, quality of life, an orientation of hope and personal meaning also improves adherence to treatment recommendations (19).

Data Collection

The population included all advanced MBC patients diagnosed before 1998 who received chemotherapy under the Center’s supervision. To accurately represent the characteristics of those seeking integrative care, all consecutive cases of advanced MBC presenting during the study period were included in the study. The inclusion criteria did not specify any minimum survival time, and thus no patients were excluded. Patients with MBC typically arrived at the Center after disease progression, through various referral sources. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board.

Data for the study included information from patients’ radiological, laboratory and pathology results, key surgical and clinical reports. Data were extracted from medical charts and evaluated in 1998 and again in 2002. An author (DT) not on the Center’s staff, who specializes in breast cancer research and treatment, reviewed study data and confirmed dates of metastasis and recurrence. Relevant data and reports from subjects’ charts, including scans and laboratory tests were inspected and analyzed. Prognostic factors (lymph node and estrogen receptor status and tumor size) were obtained from biopsy, radiological, surgical, laboratory reports, consultation reports and clinical chart notes. Data on onset and location of metastases were obtained from pathology reports, bone scans, x-rays, CT scan reports, consultation reports and medical chart notes. Demographic characteristics and treatment and recurrence dates were also obtained.

Survival time from onset of distant or systemic metastasis (i.e., metastases other than ipsilateral or contralateral lymph nodes or breast) through 2002 was determined from patients’ hospital and medical records, and confirmed through consultation with the National Death Index and other records in publicly accessible databases.

Data Analysis

Data were obtained on 90 consecutive MBC patients treated with the BCICT protocol. Dates of initial diagnosis ranged from 1975 to 1997, whereas dates of diagnosis with metastatic disease ranged from November 1984 through December 1997. A Kaplan–Meier survival curve was generated from time of diagnosis of metastatic disease. Median survival time and corresponding 95% confidence intervals were computed. To characterize the relationship of survival to prognostic variables, potential predictors of survival were selected: tumor size and number of positive lymph nodes at initial diagnosis, estrogen receptor status, age at diagnosis with metastatic disease, disease free interval, location of metastatic sites, pathological type, whether adjuvant chemotherapy was recommended and the date of implementation of the BCICT program and dietary change. The SAS statistical package was used for data analysis. The log rank test was used to compare survival distributions between different predictor variable states, and Cox proportional hazards modeling was used to assess contributions of different variables to survival outcomes.
RESULTS

Demographic and Clinical Characteristics

Demographic, tumor pathologic, hormonal and other characteristics of the 90 consecutive MBC patients are summarized in Table 1. In the study population, 3% were initially diagnosed with Stage IV disease, while 97% entered the program with systemic metastases that developed after initial diagnosis with Stages I, II, or III disease. Patients had an average of 1.8 previous chemotherapy treatment regimens before presenting at the BCICT (range 0–4); fifteen patients had undergone unsuccessful high-dose chemotherapy with bone marrow transplant. Other than two patients, all received their adjuvant chemotherapy at other centers, prior to developing progressive disease and seeking treatment at the Center. The adjuvant regimens most commonly received were cyclophosphamide, doxorubicin and 5-flurouracil (CAF), cyclophosphamide, methotrexate and 5-flurouracil (CMF) and cyclophosphamide and doxorubicin (AC). Nearly half the population had not received prior chemotherapy for metastatic disease (first-line patients, \( n = 43 \)), while smaller numbers presented for second-line \( (n = 25) \) or third-line \( (n = 22) \) therapy. The most commonly applied first-line protocols at the Center were paclitaxel and doxorubicin, paclitaxel and vinorelbine, and CAF. The most common second- and third-line protocols were doxorubicin and vinorelbine, and docetaxel and vinorelbine. Table 1 summarizes conventional treatments received by the patient population.

Survival

Median survival after metastasis in the BCICT population was calculated from a Kaplan–Meier curve (Fig. 1). Data from 12 patients in the population were right-censored: six patients were lost to follow-up and the remainder were alive at the end of the study period. The patients lost to follow-up had all survived at

<table>
<thead>
<tr>
<th>Characteristics of study population</th>
<th>90 (100)</th>
<th>Treatment characteristics</th>
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<tbody>
<tr>
<td>Treatment before BCICT</td>
<td></td>
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<tr>
<td>Surgery</td>
<td></td>
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<tr>
<td>Mastectomy</td>
<td>71 (79)</td>
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<td>Lumpectomy</td>
<td>16 (18)</td>
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<tr>
<td>None</td>
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<tr>
<td>Adjuvant chemotherapy</td>
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<td></td>
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<tr>
<td>Given or recommended</td>
<td>66 (79)</td>
<td></td>
</tr>
<tr>
<td>Not given or not recommended</td>
<td>18 (21)</td>
<td></td>
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<tr>
<td>Hormonal treatment</td>
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<td></td>
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<tr>
<td>Tamoxifen</td>
<td>50 (55)</td>
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<td>Radiation therapy</td>
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<tr>
<td>High-dose chemotherapy/</td>
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<td>bone marrow transplant</td>
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<tr>
<td>Yes</td>
<td>15 (17)</td>
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<tr>
<td>No</td>
<td>75 (83)</td>
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<td>Initial chemotherapy treatment</td>
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<td>sought at BCICT</td>
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<tr>
<td>First-line</td>
<td>43 (48)</td>
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<tr>
<td>Second-line</td>
<td>25 (28)</td>
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<tr>
<td>Third-line or later</td>
<td>22 (24)</td>
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<tr>
<td>Pathology</td>
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<td>Infiltrating ductal carcinoma</td>
<td>61 (67)</td>
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<tr>
<td>Lobular carcinoma</td>
<td>9 (10)</td>
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<tr>
<td>Phyllodes</td>
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<tr>
<td>Unavailable</td>
<td>18 (20)</td>
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<tr>
<td>Pregnancy and menopause</td>
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<td>Pregnant at or after</td>
<td>4 (4)</td>
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<tr>
<td>initial diagnosis</td>
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<tr>
<td>Presumed menopausal status* at initial diagnosis</td>
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</tr>
<tr>
<td>Premenopausal</td>
<td>71 (79)</td>
<td></td>
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<tr>
<td>Postmenopausal</td>
<td>19 (21)</td>
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Values are expressed as \( n \) (%).

*Premenopausal, age \( \leq 50 \); postmenopausal, \( >50 \).
least 41 months at the time of last contact. The median survival time from metastasis was 38 months (range 7–137 months, 95% CI 27–48). The 3-year survival was 52% while the 5-year survival was 27%. The log-rank test was used to compare median survival times of patients stratified by prognostic factors. Median survival times do not differ significantly among prognostic subgroups (number of positive lymph nodes, estrogen receptors, size of primary tumor, adjuvant chemotherapy, age at metastatic disease/recurrence, disease free interval (DFI) or metastatic site) except for estrogen receptor status (p < 0.03) and DFI; DFI of more than 18 months had significantly longer survival than those with shorter DFI (log-rank test, $\chi^2 = 7.2$, df = 1, p = 0.007). Percentages of patients in the prognostic subgroups are shown in Figure 2.

Median survival of patients in the Block Center’s population under age 40 at diagnosis of metastatic disease was not different from those aged 41–50 or those over age 50 (p > 0.32); median survival of MBC patients who were age 40 or under at initial cancer diagnosis was also similar to that of patients over age 40. In the proportional hazards model of prognostic factors in the Center population, however (not shown), DFI < 18 months, age group (<40, 41–50, >50) and estrogen receptor status (positive or negative) significantly predict survival.

The median survival from onset of metastasis of patients initially presenting for first-line treatment was 39 months; survival of second-line patients was 30 months and survival of third-line or later patients was 42 months. Corresponding 5-year survivals were 30%, 16% and 18%. Median time from diagnosis of metastatic disease to presentation at the Center (lag time) was 8 months (20). First-line patients had a median lag time of 3 months, second line patients of 13 months and third-line or later patients 15 months. First-line patients may thus be more comparable to patients in studies at other centers.

Comparison to Other Studies of MBC Patients

The BCICT population was compared with those of Clark et al. (21) and Anderson et al. (22) These studies, which evaluated chemotherapy patients treated at community clinics, provided both detailed data on proportions of patients with specific prognostic factors and survival data for prognostic subgroups. The purpose of the comparison was to determine whether the BCICT population differed substantially from other community-based clinics in prognostic variables and whether survival was comparable for prognostic categories. Patients in Anderson’s study ($n = 407$) all received chemotherapy at a single clinic. Anderson reports prognostic variables and survival after distant or systemic metastasis (defined as metastases other than ipsilateral or contralateral lymph nodes or breast). Dates of original diagnosis in the Anderson population ranged from 1958 to 1995, while dates of recurrence ranged from 1974 to 1998. Survival for the BCICT population is calculated from the time of distant or systemic metastasis as defined by Anderson et al. Patients in Clark’s study ($n = 1015$) had their estrogen receptor status evaluated by a single institution and received chemotherapy at several community clinics. Clark reports prognostic variables and survival after first recurrence (loco-regional or distant metastasis) (21). Dates of original diagnosis ranged from 1971–1983. The Clark population thus includes earlier staged patients with contralateral breast metastases (i.e., not distant or systemic metastases). This population was treated prior to the development of therapeutic advances such as taxanes, and thus could be expected to have worse therapeutic outcomes. For this reason detailed survival comparisons will be made mostly with the Anderson group, while the Clark group will be used to compare profiles of prognostic variables. The Anderson and BCICT populations both include patients diagnosed after taxanes became available.
Figures 2a–g show that the three populations were generally similar on prognostic variables. However, more of the BCICT patients had received adjuvant chemotherapy, considered an adverse prognostic factor (23). Furthermore, the BCICT population was considerably younger, a factor associated with higher risk of death after metastatic disease (24); in particular, breast cancer patients under age 40 have a worse prognosis than older patients (25). The BCICT population had more patients with bone metastases, similar numbers with visceral metastases (e.g., lung, liver) and fewer patients with regional or soft tissue metastases (e.g., chest wall, pectoral muscles, skin, supraclavicular lymph nodes, which have more favorable prognoses) than the comparison populations. These factors suggest no clear selection bias in favor of BCICT patients.

The median survival of MBC patients reported by Anderson (22) was 20 months, (Fig. 2h); the median survival of the Clark population (21) was 23 months, possibly higher due to the inclusion of earlier-staged patients with contralateral breast recurrences in this
group; while the median survival of BCICT patients was 38 months. The 5-year survival of the entire BCICT population was 27%; that of the Anderson group was 17%. Median survivals of patients stratified by prognostic subgroups were uniformly higher in the BCICT population than in the Anderson. Survival of BCICT patients with bone metastases \((n = 37)\) was 40 months (Fig. 2h), longer than similar patients of Anderson (median survival 23 months, \(n = 130)\). Survival of BCICT patients with visceral disease (lung and liver disease) \((n = 35)\) was 37 months (Fig. 2h), longer than that of Anderson patients with visceral disease (median survival 13 months, \(n = 193)\). Survival of BCICT prognostic subgroups were also longer than those of the Clark population; e.g., median survival of Clark bone metastasis patients was 19 months (Fig. 2h). Year of diagnosis may be an important factor determining survival (26). Median survival of MBC patients diagnosed after 1990 (after which taxanes became available) in the Anderson population was 15.8 months. Median survival of BCICT patients diagnosed with MBC after 1990 was 32 months \((n = 80)\).

**DISCUSSION**

Overall survival for patients with metastatic breast cancer is limited. Even the more recent taxane-based regimens and HER2-targeted therapy have yielded only modest improvements (5). The limited success in treating advanced MBC, together with the lack of standard treatment regimens, underscores the need for innovative treatment strategies.

We present a comprehensive analysis of MBC patients who received chemotherapy in the context of comprehensive integrative cancer treatment in a community setting, consisting of therapeutic nutrition with an antioxidant-rich low-fat diet high in whole grains, legumes, vegetables and fruits, individualized supplementation, prescriptive fitness training and a personalized mind-spirit program in addition to outpatient chemotherapy. This case series is the first report of BCICT survival in clinical trials restrict eligibility criteria and may exclude patients with poor performance status or short projected survival. These criteria introduce selection bias favoring improved clinical outcomes, but limits generalizability. In contrast, the present consecutive case series analysis reports outcomes for all of the Block Center’s MBC patients, regardless of performance status or projected survival, who received integrative cancer treatment with chemotherapy during the study timeframe.

We compared prognostic factors and survival of the BCICT population with Clark’s (21) and Anderson’s (22) populations, noting similar to less favorable prognostic factors for the BCICT group, but more favorable survival. Survival comparisons can also be made with other populations with similar prognostic features in the same geographic region (27), diagnosed at similar dates. For example, Chia et al. (28) reported survival of successive population-based cohorts of metastatic breast cancer patients from British Columbia. Those diagnosed in 1991–1992 had a median survival of 14.6 months; those diagnosed in 1994–1995 survived 15 months, and those diagnosed in 1997–1998 survived 18.8 months. Recurrent breast cancer patients from Texas who were diagnosed in 1990–1994 (24) and who participated in clinical trials of breast cancer drugs had a median survival from diagnosis of 27 months. This population, however, included non-metastatic patients with local recurrences, who would have substantially better prognoses than patients studied in the BCICT population. It also had fewer node-negative cases and more with visceral metastases.

Spiegel reported mean survival of MBC patients in a support group trial as 36.6 months (29); mean survival for BCICT patients, on the other hand, was 48 months \((SE = 3.7)\), despite this population having more advanced disease and more extensive prior treatment than that of Spiegel. In a more recent study, Spiegel reports a median survival of 32.8 months for patients in a support group trial recruited from 1991 to 1996 (30). There was no difference in survival of the control and support group patients. This survival is much closer to that of BCICT patients, and represents a trial in a group clearly interested in alternative treatments. Spiegel’s population had better prognostic factors including lower percentages of ER- patients \((21.4\%\) control arm/21.0\% treatment arm versus 35\% in BCICT), patients who received adjuvant chemotherapy \((50.8\%/45.3\%\) versus 79\%), patients presumed premenopausal at metastasis \((42.6\%/39.1\%\) versus 69\%), patients with visceral metastases \((31.1\%/28.1\%\) versus 38\%), a higher mean age at recurrence \((50.9\) years/51.3 years versus 46 years) and a longer time to disease recurrence \((DFI 44.5\) m/47.7 m versus 35 m) than the BCICT population. It is interesting to note that over 40\% of the
control patients (but only 20% of support group patients) attended outside support groups, a phenomenon termed “compensatory equalization” (31) in which distressed control group patients attempt to obtain a study intervention they were not assigned. Spiegel does not report whether study subjects also sought out dietary, exercise or other integrative care interventions, although such therapies are popular in California, the location of the study.

Study limitations include a potential for inconsistent data entry in medical charts. However, we included all patients treated, and emphasized objective measures and cross-checking of data sources. Standardized data collection forms were used, and exhaustive analyses of pathology and radiological scans, with clinical record reviews were performed independently by a non-BCICT investigator. One factor that could introduce bias is that the Center’s patients were a self-selected group, most of whom sought treatment after the diagnosis of metastases, and who were able to seek another opinion and/or travel. This could have enriched numbers of patients with more indolent disease. However, major prognostic indices, such as hormone receptor positivity, tumor size and DFI were not different from the historical populations compared, while other indices such as age and prior adjuvant chemotherapy were less favorable in the BCICT group. Comparing the BCICT group to historical controls is a less effective means of determining treatment effects than a randomized trial, which would reduce the ambiguities of comparing populations with differing prognostic factors.

Adherence to each component of the integrative therapies was systematically addressed at clinical visits, and documented in charts, but was not analyzed for this study. A previous study of metastatic patients treated at the Center who had survived 8 years or more confirmed long-term adherence to the program’s comprehensive nutritional and lifestyle recommendations. Daily vegetable intake was high, as was the regular consumption of whole grains and legumes. Recommendations for fish intake were followed, and refined foods were nearly eliminated while red meats were avoided entirely. Adherence to supplement exercise and mind-spirit regimens was high (12).

Breast cancer patients who ate a diet high in vegetables and fruits and also maintained a higher level of physical activity were recently reported to have a mortality rate about half that of those who ate fewer plant foods or exercised less (32). This finding highlights the potential benefits of comprehensive lifestyle interventions, and suggests that the extended survival of Center patients is physiologically based, and not simply an effect of self-selection. The recent finding of improved relapse-free survival in patients assigned to a low-fat diet in a large randomized trial (33) is of particular interest in relation to the low-fat eating plan of the Center. Other specific factors that may contribute to prolonged survival or treatment tolerance in the BCICT program include increased intakes of antioxidants and phytochemicals (34), improved body composition and weight reduction due to increased exercise (associated with a 50% decrease in mortality for 3–5 hours weekly of moderate exercise) (35), reduction of stress hormones with mind-spirit interventions (36), lower overall dietary intake of fat (29,37), and higher vegetable (38), fiber (39) and omega-3 fatty acid intake (40).

BCICT supplements are selected to assist in normalizing the internal biochemical milieu based on laboratory testing for nutritional deficits (41) and cancer-promoting factors including oxidative stress (42), inflammation (43) and abnormal blood glucose regulation (44). Molecular testing including but not limited to EGFR, VEGF, pAKT, and COX-2 expression in patient derived tissue and blood is also used in selecting high quality supplements, while other supplements are coupled to specific medical protocols to mitigate disease- and treatment-related symptoms and enhance treatment response and outcomes (45,46). The potential utility of BCICT supplements is being evaluated through sponsored research at leading cancer research centers such as the University of Texas M. D. Anderson Cancer Center. This has resulted, for example, in original observations of the effects of specific fish oils that are not only capable of reducing COX-2 enzymatic activity but which can also give rise to PGE$_3$, an eicosanoid that counters the inflammation associated with overproduction of COX-2 and its substrate, PGE$_2$, with corresponding tumor regression (47). Such research is needed to elucidate the scientific rationale supporting inclusion of supplements in the nutrition component of the integrative cancer treatment program.

This consecutive case series, the first assessment of chemotherapy patients undergoing integrative cancer treatment, reports substantially favorable survival outcomes for metastatic breast cancer patients using comprehensive interventions employing both conventional and complementary therapies. The survival time
observed for the BCICT group was approximately double or possibly higher than that of most comparison populations, despite the substantial percentage of younger and relapsed patients in the population. Five-year survival was 27% for BCICT versus 17% for comparison patients. The demographic, prognostic and outcome data presented here will contribute to the design of future trials. Randomized trials are needed to show more conclusively the impact of the total BCICT program on patient survival, but are not without major challenges. Designing an adequate control condition for subjects willing to participate in trials of a major lifestyle change is perplexing, and compensatory equalization (31) could well become problematic. Patients would need to be randomized to receive chemotherapy with or without integrative treatment. Single interventions that are part of the BCICT program may not have an effect size large enough to detect their impact statistically in a clinical population. Thus, future research should be conducted on the entire BCICT system of therapeutic nutrition and supplementation, prescriptive fitness and physical therapy, and personalized mind-spirit care.

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