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Lack of Patient Compliance with Adjuvant Therapy Guidelines is an Important Risk Factor for Recurrence in Early Breast Cancer

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Background: A retrospective three-year study identified 383 patients referred for treatment of recurrent breast cancer relapse, following previous primary treatment of early stage breast cancer. Details of their primary treatment were recorded to determine if their initial treatment complied with current National Comprehensive Cancer Network (NCCN) guidelines.

Patients and Methods: The original medical records of patients referred to Cancer Treatment Centers of America at Midwestern Regional Medical Center (CTCA/MRMC) with recurrent breast cancer were reviewed. Approval from our Institutional Review Board (IRB) was not required as this was a retrospective record review.

Results: a total of 222 patients completed all treatment consistent with current NCCN guidelines, while 161 patients did not. 11 patients declined the recommended surgery, while 66 of the 299 patients refused the recommended radiation therapy. 354 patients received appropriate adjuvant chemotherapy.

74 patients either declined adjuvant chemotherapy or failed to complete the recommended course of chemotherapy treatment. Nearly forty percent of patients (102/261) either declined or terminated hormone treatment before receiving a full five years of therapy. Over 63% of the patients who were recommended adjuvant Herceptin (24/38) completed a full 12 months of treatment. Patients with negative nodes or 1-3 nodes involved were more likely to have received inadequate treatment when compared with those who had 4-9 or 10 or more nodes involved.

Conclusions: This study confirms that patients are more likely to refuse adjuvant drug treatment than surgery or radiation, and that refusal of treatment is associated with an increased risk of disease recurrence.

INTRODUCTION

Modern treatment of patients with early stage breast cancer requires a combination of multi-disciplinary treatments, which generally includes surgery, radiation, and some form of adjuvant drug therapy (chemotherapy, hormones and/or

Herceptin depending on the biologic characteristics of the tumor). Detailed treatment guidelines for the treatment of early breast cancer have been developed and have been validated in numerous randomized clinical studies [1-4]. Despite this experience, numerous previous reports have described varying degrees of patient non-compliance with treatment recommendations [5-11]. We have previously described a cohort of patients with early stage breast cancer who either delayed seeking medical treatment despite obvious symptoms, or refused

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treatment despite a positive biopsy [12]. Based on that experience we questioned how many of our patients with relapse of early stage breast cancer had not completely followed the treatment recommendations of their primary oncologists.

Patients and Methods

To evaluate the incidence and significance of patient non-compliance with recommended treatment guidelines for early breast cancer, we retrospectively studied all patients with recurrent breast cancer seen by Dennis L Citrin (DLC) or Registered Nurse (RN) during the three-year period July 1 2009 through June 30 2012.

To be included in this review, all patients had to fulfill the following criteria:

1. An initial diagnosis of early stage breast cancer (defined as stage 1-3 disease) and definitive treatment with curative intent at an outside facility.
2. Referral to CTCA/MRMC after a confirmed diagnosis of recurrent breast cancer.
3. All previous medical records (including pathologic slides from primary diagnosis) available for review.

Patients with systemic metastases (stage 4) or inflammatory breast cancer at the time of initial diagnosis and treatment were not eligible for this study. In eligible patients, the details of the initial pathologic stage and grade of the primary tumor, Estrogen Receptor/Progesterone (ER/PR) and Human Epidermal Growth Factor 2 (Her2) neu positive status, and details of all primary treatment were recorded. Additionally time to first recurrence and sites of recurrence were recorded.

CTCA/MRMC IRB was notified of this retrospective study and it was determined that ethical approval and patient consent was not needed.

Definitions of Adequate Treatment

The following criteria for adequacy of treatment were used

Surgery: Excision of primary tumor to achieve clean surgical margins and sentinel node biopsy. In patients with positive sentinel node biopsy, an axillary node dissection was also required.

Radiation: In patients having breast-conserving surgery, partial or total breast irradiation was required. In mastectomy patients, radiation to chest wall, axilla and supra-clavicular areas was required if 4 or more nodes were positive for metastatic cancer.

Chemotherapy: Where adjuvant chemotherapy was indicated according to current NCCN guidelines, adequate treatment was defined as 4 cycles of an Anthracycline containing regimen followed by 4 cycles of a Taxane, or equivalent regimen.

Hormone therapy: In ER positive patients 5 years of adjuvant hormone therapy were considered adequate.

Herceptin: In Her2neu positive patients 12 months of adjuvant Herceptin were considered adequate. Initial treatment was coded as either adequate (category A) or inadequate (category B), based on whether it was consistent with current NCCN guidelines.

Table 1: Size of Primary Tumor Patient Compliance

Size of Primary Tumor	#pts
Tx	13
T1	145
T2	170
T3	53
T4	2
Total	383

Results

Three hundred and eighty three patients with recurrent breast cancer were identified during the study period. Their median age was 46 (range 24-80). Two hundred and sixty one were Caucasian (67.8%), one hundred and one were African-American (26%), twenty two were Hispanic (6.7%), and one patient was Asian American (0.2%).

Stage at time of first diagnosis

Size of primary tumor and nodal status at time of first diagnosis are shown in Tables 1 and 2.

Two hundred and sixty one patients (68%) had ER positive, and sixty one patients (18%) had Her2neu positive tumors.

Two hundred and twenty-two patients (58%) completed all of the treatment considered standard treatment at the time and recommended by their treating physicians, while one hundred sixty-one (42%) did not. There was no significant difference between the incidence of non-compliance in Caucasian and African-American patients (41% compared with 44.6%; Chi Square P = 0.76).

Patient Compliance by Treatment Modality

Eleven patients declined the recommended surgery (Table 3), while 66 of the 299 patients (23.8%) refused the recommended radiation

Table 2: Nodal Status

Number of Nodes Involved	#pts
None	137
1 to 3	124
4 to 9	69
10 or more	40
Unknown	13
Total	383

Table 3: Patient Compliance by Treatment Modality

Treatment	Indicated	Compliant	Non-compliant
Surgery	383	372 (97.1%)	11 (2.9%)
Radiation	299	233 (77.9%)	66 (22.1%)
Chemotherapy	354	280 (79.1%)	74 (20.9%)
Hormone Therapy	261	159 (60.9%)	102 (39.1%)
Herceptin	38*	24 (63.2%)	14 (36.8%)

* 23 of the 61 Her2 positive patients were treated before adjuvant Herceptin became the standard of care, and were not offered Herceptin. Patient compliance with physician recommendation was therefore evaluated in 38 Her 2 positive patients.

therapy. Three hundred fifty-four patients received appropriate adjuvant chemotherapy. Seventy-four patients (20.9%) either declined adjuvant chemotherapy or failed to complete the recommended course of chemotherapy treatment. Nearly 40% of patients (102/261) either declined or terminated hormone treatment before receiving a full five years of therapy. Over 63% of the patients who were recommended adjuvant Herceptin (24/38) completed a full 12 months of treatment (Table 3). Many patients refused more than one treatment modality, as shown in Table 4.

Patterns of Treatment Refusal

Seven of the eleven patients who did not receive adequate surgery refused any surgical treatment, while two declined re-excision which was recommended because of involved margins, and two refused axillary lymph node biopsy. Sixty-three patients refused recommended radiation treatment, while three terminated radiation before completing the full recommended course. Of the seventy-four patients who did not receive adequate adjuvant chemotherapy, fifty-one (68.9%) refused all chemotherapy while 23/74 (31.1%) patients received some chemotherapy but did not complete the recommended treatment program. A similar pattern was seen with hormone therapy, where sixty-six of one hundred-two (64.7%) patients refused any treatment, while thirty-six patients (35.3%)

Table 4: Patient's Refusal of Treatment Modalities

Treatment Modalities Refused	# of Patients
1	61 (37.8%)
2	61 (37.8%)
3	25 (15.5%)
4	11 (6.8%)

terminated hormone treatment prematurely. Of these, twenty-seven stopped Tamoxifen, while nine stopped taking an Aromatase Inhibitor.

Effect of Inadequate Surgery and Radiation on Local Recurrence

As might be expected, there was a high incidence of loco-regional recurrence in those patients who refused adequate surgery and radiation therapy. All of the seven women who initially refused any surgical treatment and forty-nine of the sixty-six patients who refused radiation therapy (74%) had evidence of significant loco-regional disease when they came to CTCA/MRMC (Table 5).

Adequacy of Initial Treatment and Nodal Status

When the entire cohort of three hundred eighty-three patients was evaluated for the effect of adequacy of treatment on chance of relapse, it was found that those patients with negative

Table 5: Relation between Loco-Regional Treatment and Sites of Relapse

	Patients Declined Surgery	Patients Declined Radiation
Loco-Regional Disease	3	29
Both Loco-Regional Disease & Systemic Mets	4	20
Systemic Mets Only	4	17
Total	11	66

Table 6: Relationship between Nodal Status and Adequacy of Treatment

Nodes Involved	#pts	Adequate Treatment	Inadequate Treatment
Unknown	13	2 (15.4%)	11 (84.6%)
0	137	68 (49.6%)	69 (50.4%)
1 to 3	124	70 (56.5%)	54 (43.5%)
4 to 9	69	51 (73.9%)	18 (26.1%)
10+	40	31 (77.5%)	9 (22.5%)
Total	383	222	161

nodes or 1-3 nodes involved were more likely to have received inadequate treatment (50% and 43.6% respectively) when compared with those who had 4-9 (26.1%) or 10 or more nodes involved (22.5%) (Chi Square P = 0.011) (Table 6). The high incidence of inadequate treatment in those patients whose nodal status is unknown is due to the fact that most of these patients refused axillary node biopsy.

Discussion

Our experience is consistent with previous reports, which indicate that patients with early stage breast cancer frequently refuse treatment [5-12]. In this study, patients were generally very accepting of the need for surgery, but were less likely to agree to radiation and systemic treatments. Many patients declined more than one treatment modality. Previous reports have indicated that patient non-compliance is more commonly seen in minority patients, patients from lower socio-economic groups, younger women and patients treated in community hospitals rather than university hospitals [13-15]. In our study population at least, there was no significant difference between the incidence of non-compliance in African-American and Caucasian patients. No attempt was made in this retrospective study to identify socio-economic factors or location of prior therapy, but based on our referral experience it is likely that the majority of our patients did not receive their primary treatment in university hospitals. It

appears that patient failure to comply with recommended treatment is not unique to any particular demographic group, and appears to be a universal phenomenon, which has been reported in European and African countries, in addition to the United States [16, 17]. Because this was a retrospective study of patients who relapsed (treatment failures), it is not possible to determine the precise clinical significance of patient non-compliance in contributing to treatment failure. However, the incidence of non-compliance was significantly higher in those patients with negative axillary nodes or minimal nodal disease (one to three nodes involved), when compared with patients with 4 or more nodes involved. These are the very patients where a high probability of cure could otherwise be reasonably anticipated. Several conclusions may be drawn from this fact. First, the current standard of care for patients with extensive nodal involvement is frequently inadequate in preventing future relapse. Second, patient refusal of treatment is associated with an increased risk of disease recurrence. All of the patients in the present study suffered a recurrence of their disease; our experience in this regard is consistent with previous studies which demonstrated that patient non-compliance is clearly associated with poorer outcomes [12, 18, 19]. This retrospective study did not attempt to address the *reasons* for patient non-compliance. It has been previously reported that side-effects of endocrine treatment was a major cause of women prematurely discontinuing Tamoxifen and Aromatase Inhibitors [20]. In this study however, nearly two thirds of the patients who refused chemotherapy and hormone therapy did so without any exposure to treatment. This indicates that *fear of toxicity* and not actually experiencing side-effects is more commonly the cause of patient refusal, at least in this patient population. We believe that a significant percentage of women with early breast cancer have pre-conceived beliefs which make them more likely to reject conventional cancer treatment in favor of alternative forms of treatment [21]. These beliefs are often reinforced by what patients often consider less than

sympathetic interactions with physicians [12]. It is the responsibility of physicians to inform and educate women regarding the rationale for, and the efficacy and value of modern multi-modality breast cancer treatment, and to do so in a way that is respectful of the patient and her beliefs. As the highest incidence of patient non-compliance occurs with systemic treatment, this is generally the responsibility of the medical oncologist. Adjuvant systemic therapy presents a unique challenge, as it is given to women with no evident disease, and patients cannot see any clear evidence of benefit while they are receiving such treatment. It may appear almost counter-intuitive in that patients who receive adjuvant treatment often feel worse than those who do not. Patient non-compliance is most commonly seen with hormone therapy, and our experience is very similar to previous reports in this regard [10, 20, 22, 23]. The major reasons for the high incidence of patient non-compliance with adjuvant hormone therapy is the long duration of treatment (five or more years), in contrast with other treatment modalities. Also, patients have less interaction with their health care providers during the five years of hormone treatment and often experience undesirable side-effects of endocrine treatment (hot flashes, arthralgias, weight gain, loss of libido) while the potential benefit (reduced risk of future disease recurrence) is less obvious. Attempts have been made to improve patients' compliance with systemic adjuvant therapy by developing specific support programs and using patient navigators [24-28].

We have found that www.adjuvantonline.com provides a useful a graphic educational tool that clearly demonstrates to the patient the benefits of adjuvant therapy [29].

Whatever informational tool is used, it is clear that it is the responsibility of the medical oncologist to clearly inform the patient of the risks and benefits of adjuvant therapy, and there remains a continuing need for patient education

and encouragement throughout their course of treatment.

Conclusions

We have made tremendous strides in developing and refining adjuvant therapy over the past thirty years. Our study and several others have confirmed that many women deny themselves the benefit of such treatment. Of particular concern, almost half of all women with ER positive breast cancer continue to receive inadequate endocrine therapy, with clearly deleterious effects. More efforts are needed to identify and correct the factors which contribute to this phenomenon.

Abbreviations

NCCN: National Comprehensive Cancer Network

DLC: Dennis L Citrin

RN: Registered Nurse

CTCA/MRMC: Cancer Treatment Centers of America at Midwestern Regional Medical Center

IRB: Institutional Review Board

ER: Estrogen Receptor

PR: Progesterone Receptor

Her2: Human Epidermal Growth Factor 2

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

DLC was the lead investigator of this study and provided; the concept and design, patient/data collection, interpretation of the data, drafting of the manuscript, final approval to be published. **SJM** managed patient information, data analysis and final revisions of manuscript.

RN provided patient/data collection.

JFG provided concept and design, data analysis and interpretation, final revisions of manuscript.

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