SEQUENTIAL THERAPY IN METASTATIC BREAST CANCER: SURVIVAL ANALYSIS WITH TIME DEPENDENT COVARIATES

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SEQUENTIAL THERAPY IN METASTATIC BREAST CANCER: SURVIVAL ANALYSIS WITH TIME DEPENDENT COVARIATES

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Metastatic breast cancer, a disease with a high mortality rate among women, is a major public health problem in the United States and other developed countries. This study evaluated the effect of certain treatments within the clinical setting during the patients' individual courses of sequential treatments. A database based on clinical data from one practice of the University of Pittsburgh Cancer Institute Breast Cancer Program was used to analyze from data metastatic breast cancer patients receiving sequential therapies. Data from the clinic cohort were available from January 1999 to July 2005.

Taxanes, a specific class of chemotherapeutic agents including Taxol® and Taxotere® have been demonstrated to be very effective in tumor control and symptom relief in metastatic breast cancer patients. However, it is unclear whether there is a benefit in survival compared to non-taxane compounds. Therefore, the survival among patients who received taxane-containing regimes versus those who never received taxane-containing regimes as chemotherapeutic agents needs attention.

The purpose of this study is to investigate the survival benefit of taxanes, after initiating chemotherapy or hormonal therapy. Hence, survival analyses with time dependent covariates were employed. The results showed that taxane was beneficial for survival in women with metastatic breast cancer. However, the effect strongly depended on the estrogen receptor type. Patients who had metastatic breast cancer with negative

estrogen receptors benefited from taxane therapy. In contrary, taxane showed an adverse effect in patients with positive estrogen receptor cancer. The combination of toxic side effects from the drug, patient characteristics, and timeline of taxane intervention might have possibly contributed to this finding.

These results will facilitate the development of guidelines for the management of metastatic breast cancer. In the meantime it will be useful to guide clinicians in their decision-making regarding therapeutic regimes for metastatic breast cancer providing physicians and health care professionals with an important tool to improve public health.

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1   INTRODUCTION

Metastatic breast cancer is a disease with a high mortality rate among women and its personal, social, and economic impacts are a serious public health burden. This study evaluated the effect of therapeutic agents during the course of sequential treatments that are multiple lines of therapy for metastatic breast cancer within the clinical setting based on the state of the art clinical practice.

1.1   Breast cancer

Breast cancer is the most common female cancer and the second leading cause of cancer-related deaths among women in the United States (Tierney et al., 2005). Among women, a total of 211,240 new breast cancer cases and 40,140 deaths are expected in the United States in 2005; this corresponds to 32% of all cancer incidences and 15% of all cancer-related deaths (Jemal et al., 2005). The probability of developing invasive breast cancer in a woman's lifetime is 13.4%; that is 1 in 7 women are at risk (Jemal et al., 2005).

Gender is the major risk factor for breast cancer; women are 100 times more likely to develop breast cancer than men (American Cancer Society, 2005). Among women, the most important risk factors are family history, age at menarche, age at menopause, age at first life birth, and parity (American Cancer Society, 2004). Race is a factor in breast cancer; white women have a higher incidence and African-American women a higher mortality. Specifically, the estimated incidence of invasive breast cancer is 82% in white women, 9.5% in African American women and 8.5% in women of other minorities. Among all estimated female breast cancer mortalities, the estimated deaths are 79.6% in white women, 14.3% in African American and 6.1% in other minorities (Jemal et al., 2003). The relative survival rate is lower among African American women than

white women; with a 32% higher death rate (Jemal et al., 2003). Age is a major risk factor for breast cancer, although younger women often suffer from severer and stronger genetically linked forms of breast cancer. However, younger women have been shown to remain in remission longer than older women for metastatic disease (Greenberg et al., 1996).

Over the years treatment has become more effective, improving long-term survival. Many women survive for several years after diagnosis. However, the prognosis for these patients is poor if the cancer cells have metastasized to distant sites. About 10% of women present with metastatic disease at their initial diagnosis of breast cancer (Overmoyer, 1995). A substantial number of women (20-85%) develops metastatic disease at a later time, often many years or even decades later (Greenberg et al, 1996). Survival may vary dramatically depending on the location of the metastasis; the average survival time with metastatic disease is 2 to 3 years (McEvilly and Dow, 1998). The median survival time ranges from 18 to 24 months (Stockler et al., 2000).

Currently there is no cure for metastatic breast cancer. Therefore treatment goals are different for these patients compared with local disease. The therapeutic goals are disease control and the relief of symptoms (palliation) depending on the progression of the disease and patient preference. The American Society of Oncology (ASO) recommends at least 3 sequential therapies before switching to palliative care.

1.2   Therapy

Treatment options for metastatic breast cancer include surgery, radiation, hormonal therapies, chemotherapies, vaccines, and biologic therapies. Among these therapies, chemotherapy and hormonal therapies are the most commonly administered therapies.

Their mechanisms to achieve tumor reduction or elimination differ from each other; chemotherapeutic agents destroy the cancer cell and hormonal therapeutic agents alter the cancer cells' environment. Table 1 summarizes therapies for metastatic breast cancer used in practice.

Table 1. Treatment Categories and Their Mechanism

Treatment Type	Function
Chemotherapy	destroys cancer cells
Hormonal Therapy	change the cancer cells' environment to reduce growth
Immunological Therapy	improve immune system
Vaccine Therapy	helps immune system to develop antibodies
Biologic Therapy	increases the body's own defense

The absence and presence of specific cancer receptor types strongly influence the treatment choices (Tierney et al, 2005). The most common receptors that play a key role are estrogen (ER), progesterone, and human epidermal growth factor 2 (HER-2) receptors. Hormonal therapy, also called endocrine therapy, is useful in the presence of specific receptor types. For example, cancer with positive estrogen and progesterone receptors show good response to hormonal therapy (Tierney et al., 2005).

In general, patients with receptor positive primary tumors have a more favorable prognosis. Sixty percent of patients with metastatic breast cancer respond to endocrine therapy if the cancer contains ER positive receptors (Tierney et al., 2005). Most hormonal therapies work by decreasing the amount of respective hormone or by blocking the cancer from obtaining this substance. Hormonal therapies include anti-estrogens,

aromatase inhibitors, and ovarian treatments. Table 2 presents response rates to hormonal

therapies based on management options presented by McGinn and Moore (2001).

Table 2. Description of Hormonal Therapies and Response Rates

Agent Group	Agents	Response Rate
Antiestrogen	Tamoxifen	30-40%
Aromatase Inhibitor	Aminoglutethimide	
	Anastrozole	30-40%
Progestins	Megestrol acetate	
	Medroxyprogesterone	20-40%
LHRHA	Goserelin, Leuprolide	35-40%
Estrogens	Diethylstilbestrol	
	Ethinyl estradiol	
	Conjugated estrogens	20-40%
Androgens	Fluoxymesterone	5-20%

Note: modified from Table 1 in McGinn and Moore (2001). LHRHA: Luteinizing Hormone releasing

Hormone Agonists

Hormonal therapy is recommended as first line therapy when the cancer has

estrogen receptors. Interestingly, in a recent study, Esserman et al. (2005) demonstrated

equal response to tamoxifen irrespective of receptor expression contrary to the

established finding. Furthermore, negative secondary tumors emerged in women after

tamoxifen use. However, in first line therapy, both hormonal and chemotherapy are

similarly effective in women with hormonal cancer (Stockler et al., 2000). No clinical

trials have been performed to compare survival of women with metastatic breast cancer

who received hormonal therapy. Because it has been proven that hormonal therapy has a

beneficial therapeutic effect on patient with breast cancer, it is ethically unacceptable to deny this form of therapy to patients for study purpose.

HER-2 is overexpressed in about 25 to 30% of breast cancers (Slamon et al., 2001). Women with breast cancer that overexpresses HER-2 have an aggressive form of disease. Fortunately, HER-2 receptor positive cancer responds to therapy with Herceptin® (trastuzumab). However, the combination of chemotherapies with Herceptin® has been shown to result in greater overall survival than Herceptin® alone (Slamon et al., 2001). Patients may develop congestive heart failure due to the administration of the drug, which is an indication to discontinue this therapeutic compound (McGinn and Moore, 2001).

Chemotherapy is usually recommended when the women with metastatic breast cancer have no estrogen receptor on their cancer or when hormonal therapies do not control symptoms any longer. In the United States, the commonly used chemotherpautic agents for metastatic disease are adriamycin, cyclophosphamide, and taxanes. Table 3 presents response rates to first and second line chemotherapies.

Table 3. Description of Chemotherapies and Response Rates

Agents	Response Rate	Remission Phase
1st line	35-75%	
2nd line	20%	2- to 4-years disease free survival

Note: modified from Table 2 in McGinn and Moore (2001). 1st line with cyclophosphamide, fluorouracil, doxorubicin, methotrexate, mitroxantrone, leucovorin. 2nd line with paclitaxel, docetaxel, or vinorelibine or single agent therapy with fluorouracil, paclitaxel or docetaxel.

Taxanes, a specific group of chemotherapeutic agents including Taxol®
(paclitaxel) and Taxotere® (docetaxel), have become part of standard management of
metastatic breast cancer in most Western countries and belong to the most active
chemotherapy agents used in that respect. In the clinical setting, taxanes have been
demonstrated to be very effective in metastatic breast cancer patients (Tierney et al.,
2005, Seidman et al., 1995). A systematic review and meta-analysis of Cochran Breast
Cancer Group Registry revealed that taxanes benefit in terms of overall survival (Ghersi
et al., 2005). In a review of clinical trials, overall survial was longer with taxanes
(Clemons et al., 1997). In a Phase III Clinical trial superiority of Taxotere was
demonstrated with improved survival compared to other state of the art chemotherapies
(Nabholtz et al., 1999). For taxotere, improved response was reported (Chan et al., 1999)
with median time to progression of 6.3 month compared to 3 months with the alternative
therapy (Sjöstörm et al., 1999). However, clinical trial results on taxanes as first line
treatment do not show extended survival (Bernhard-Matry et al., 2003). This highlights
the importance to evaluate the real impact of taxanes on the natural history of the disease.

There is no consensus in the literature about the effects of treatment on survival or
the relative efficacy of the combination therapy including both chemotherapy and
hormonal therapy versus hormonal therapy alone. Based on a few studies with small
sample size Stockler et al. (2000) concluded that there is no survival benefit for the
combination of hormonal therapy and chemotherapy over the individual therapy alone.
Two clinical trials comparing 1st line chemotherapy and 1st line hormonal therapy had
opposing effect (Stockler et al., 2000), nevertheless the ratio of median survival favoring

chemotherapy was higher in magnitude. Hospital based studies comparing chemotherapy and no chemotherapy yielded contradicting results (Cardoso et al., 2002).

Cardoso et al. (2002) reviewed the impact of second and subsequent lines of chemotherapy for metastatic breast cancer and found the benefits to be minimal. Although high response rates can be achieved and with it a substantial palliation, a major issue in the treatment of metastatic disease is to maintain remission. Irrespective of treatment received, after progression, crossover to an alternative treatment is recommended. For this reason, the number of sequential treatments that are number of lines of therapy received by the patient may be more than 3.

Over the recent decades, significant advances were made in therapy development for metastatic breast cancer. These developments have produced improvements in patient response and survival. In clinical practice the therapy of metastatic breast cancer is based on an individual patient performance and disease progression. To date, there is no guideline available for the optimal sequential therapy for metastatic breast cancer. This study highlighted important aspects of sequential therapies and their relation to survival.

1.3   Research Statement

This study evaluated the effect of treatments within the clinical setting during the patients' individual courses of sequential treatments. The question of interest is whether there is a differential survival among patients who received taxane-containing chemotherapeutic regimens versus those who never receive taxane-containing regimens.

The purpose of this study is to investigate the benefit of taxane therapy in metastatic breast cancer patients. Taxane-containing regimens can be administered for any sequential therapy depending on the clinical performance. The time prior to receiving

a taxane-containing regiment should not be contributed to the effect of taxane in the analysis. For this reason, I used taxane therapy as a time-dependent covariate in the analysis. The results can be useful to guide clinicians in their decision-making regarding therapeutic regimes for metastatic breast cancer.

1.4 Statistical Considerations

The current study is an observational study. Therefore, it is important to address the meaning of the results compared to a clinical trial. In contrast to a clinical trial where causal effects can be attributed to the intervention due to the randomization, for observational studies such associations must be tentative (Bull and Spiegelhalter 1997).

However, the current study questions cannot be answered in a clinical trial due to ethical considerations. Furthermore, many aspects of natural disease would need to be pre-defined and regulated, which is not feasible. As such, this observational study is relevant and meaningful to enhance the understanding of treatment management to improve survival.

Another important statistical aspect is the assumption that only non-informative censoring occurs in a study when using survival analysis (Bull and Spiegelhalter 1997). This means the patient is lost or withdraws from the study due to facts unrelated to the potential outcome. Informative right-censoring may influence the outcome and when ignored may bias the result of the study.

2 METHODS

2.1 Recruitment Procedure and Subjects

A cohort study was conducted with metastatic breast cancer patients receiving sequential therapies from one practice (five physicians at two sites) of the University of Pittsburgh Cancer Institute Breast Cancer Program. For this, the data were abstracted based on a retrospective chart review. Patients were included if they met the following inclusion criteria: 1) being female, 2) being above 18 years in age, and 3) having a diagnosis of metastatic breast cancer between January 1999 and July 2005. Second opinion visits were excluded due to inaccessibility of records. Patients who withdrew prior to end of the study (N=28), which may relate to informative censoring, were excluded. The final patient pool consisted of 379 subjects.

2.2 Data Acquisition

Patient information was acquired during each clinic visit by a personal interview. In the standard assessment procedure a form was filled. These medical records were reviewed and data abstracted into a database and double-checked. This database was made available for the use of this thesis. For the use of the historical and de-identified database to investigate the specific aims mentioned in the research statement, IRB approval was granted.

2.2.1 Data set

The data obtained from the database contained subject ID, death status at end of study, age, race, receptor status for estrogen and HER-2, location of metastasis at diagnosis, number of metastatic sites, months to metastatic disease from diagnosis of breast cancer, overall survival time from breast cancer diagnosis and survival time from metastatic

disease diagnosis, and treatment-related details for each sequential therapy, such as treatment category and, if applicable, chemotherapy and/or hormonal treatment, response to therapy measured by a scan, and performance status. Table 4 lists variables that are available at a single occurrence in time (fixed variables), which was the first visit for all variables except for age, which was obtained at diagnosis of metastatic disease and number of metastatic sites for which it was obtained at death or last follow up visit and time-dependent variables. Values for all variables are described in the Appendix.

Table 4. Description of Variables in the Database

Variables	Description
Fixed	
ID_pat	Patient ID
dead	Death status at follow up
Age	Age in years at diagnosis of metastatic breast cancer
Race	Patient Race
ER	Estrogen receptor status
Her2	HER-2/neu receptor status
LocMet	initial location of metastasis (bone or bone and visceral)
Sites	Number of metastatic sites at death or censoring
MoMet	Month from initial diagnosis to metastatic disease
BCSurv	Overall survival or time to censoring
Msurv	Survival in months from metastatic diagnosis
Time-Dependent	
T#	Overall treatment category for treatment
Tx#Chemo	Chemotherapy for treatment
Tx#Horm	Hormonal therapy for treatment
Tx#Mo	Cumulative months on treatment
Tx#Resp	Radiographic scan response to treatment
Tx#PS	Performance status at beginning of each treatment

Note: #: treatment number in sequence; e.g., T1 stands for the first therapy category received in sequence.

2.3   Statistical Analysis

To analysis the time to occurrence of an event, survival analysis is the method of choice (Cleves et al., 2004). In the current study, survival time was measured from diagnosis of metastatic breast cancer until death or the end of the study. The proportional hazards model introduced by Cox in 1972 (Cox, 1972) has been widely used for the analysis of survival data. This method facilitates the handling of censored data, that is, data with no observed outcome after a time. In conventional regression analysis observations from censored data have to be eliminated and therefore do not contribute to the analysis and the understanding of the question of interest. In survival analysis, all observations available up to the time of censoring are used in the analysis. Cox proportional hazard model is useful in addressing this topic beyond other methods in that it used regression with censored data based on minimal assumptions about the shape of the baseline hazard survival times.

For longitudinal studies during which data are collected at multiple time points, the use of the Cox proportional hazards model with time-dependent covariates is appropriate. In the present study, sequential treatment data provide additional relevant time-dependent prognostic information.

2.3.1 Cox Proportional Hazards Model With Time-Depend Covariates

According to the Cox proportional hazards model with time-dependent covariates, the hazard of death at time t for a given vector of covariates X(t) is:

$$h(t|x) = h_0(t) \exp[\beta\, X(t)] \qquad\qquad \textbf{Eq. 1}$$

$$= \begin{cases} h_0(t) & \text{with covariate } X(t)=0 \\ h_0(t)\exp(\beta) & \text{with covariate } X(t)=1 \end{cases}$$

where $h_0(t)$ is an unspecified baseline hazard function at time t and β a vector of unknown regression parameters. The time-dependent analysis takes into account the time until the event of interest occurs and the time the covariate status applies (Vittinghoff et al., 2005).

The parameter estimate vector, β, of the Cox proportional hazards model relate to hazard; and are interpreted as natural logarithm (ln) transformed hazards ratios. The interpretation of the parameter estimate depends on the values of the covariate. In general, a positive parameter estimate indicates a worse prognosis and a negative coefficient indicates a protective effect of the respective variable. The hazard ratio associated with a specific predictor variable is computed by the exponentiation of its parameter estimate.

2.3.2 Test Assumption of Proportionality

An important assumption to be tested is the proportionality assumption of the hazard rates. There are several methods to demonstrate the validity of the assumption. The most common method is computing a model including the interaction of each covariate with time in the natural logarithm scale (Collett, 1994). Significant interactions with time demonstrate a violation of the proportional hazard assumption (Klein and Moeschberger, 1997). In addition, this assumption may be assessed by plotting graphs of the $-\ln(-\ln)$ of survival probability versus survival time in the natural logarithm scale (Hess, 1995).

In case a violation of this assumption occurs, stratifying by the covariates that result in the violation is a useful method, when the covariate is not of immediate interest

to address the question of interest, because no parameter estimate will be computed for this variable after stratification.

2.4 Analysis Plan

The analysis plan consisted of evaluating variables of interest, computing descriptive statistics including Kaplan-Meier survival curves, and fitting Cox proportional hazards multivariate model including the time-dependent covariate and other fixed covariates. The significance level (α) for all analyses was 0.05 unless otherwise stated. Analyses were carried out using SAS® software version 8.2 (SAS Institute Inc., 2000). Kaplan-Meier survival graphs were produced using Stata version 9 (StataCorp., 2005).

2.4.1 Evaluation of Variables

The outcome of interest is survival, the time from metastatic diagnosis to death or censoring. All variables were considered in the survival analysis except the number of metastatic sites (*sites*) at death, response to therapy (*TX#Resp*), and the performance status evaluated at the onset of each therapy (*Tx#PS*). The variable *sites* contained the number of metastatic sites at death or censoring (data is based on information from the last follow up visit) and was not used for analysis since it co-occured with the event of interest and was expected to vary across the course of treatment. The variable *Tx#PS* recorded the performance status at the beginning of each sequential therapy were not used in the analysis due to the large amount of missing data (50.3% of all entries). Similarly, the variable *Tx#Resp*, which presented a response indicator for treatment, was affected by a substantial amount of missing data with 29.3% missing entries.

Based on clinical considerations, age was dichotomized into two categories, women below 55 years and women 55 years and older. This categorical age variable was

used in all analyses. Table 5 describes the recoding of relevant variables for analysis purposes.

Table 5. Recoded Variables for Analyses Purposes

Variable Name	New Variable Name	Value	Description
Fixed			
Age	AgeCat	1	≥ 55 years in age
		0	< 55 years in age
Race	White	1	White
		0	Non-White
ER	ERp	1	positive
		0	negative
Her2	Her2p	1	positive
		0	negative
LocMet	Bone	1	bone
		0	bone and/or visceral
MoMet	MoCat	1	> 30 months
		0	≤ 30 months
Tx1Chemo	Tx1Taxane*	1	1st line taxane therapy
		0	1st line no taxane therapy
Time-dependent			
Tx#Chemo	TaxUse*	1	after first taxane use
		0	prior to or no taxane use

Note: Missing and unknown values were recoded to SAS missing code; * among chemotherapy receivers

2.4.2 Descriptive Statistics and Univariate Survival Models

Descriptive statistics were computed for all relevant variables.

Kaplan-Meier curves were produced for all patients and by age group, race, ER status, HER-2 status, location of metastases at diagnosis, length of from initial diagnosis to metastatic disease (dichotomized for values above and below the median), and the fixed covariate 1st line therapy containing taxane. Graphs to assess the proportional hazard assumption of each covariate were also produced.

2.4.3 Multivariate Survival Model

2.4.3.1 Model Aspects and Diagnostics

Ties in the event time were handled using Breslow's method. A link test to verify that the coefficient on the squared linear covariate was not significant was performed (Cleves et al., 2004). In this way, the linearity of the variable MoMet, months to metastatic disease, was assessed. This was the only continuous variable that was entered into the model.

To assess the validity of Cox proportional hazards models, diagnostics included the proportionality assumption test, which corresponds to a model specification test, and an evaluation of influential points using Dbeta residuals.

2.4.3.2 Model Building Strategy

A backward stepwise selection method was used to determine the inclusion of variables in the final model (with a significance level of 0.15 for variable removal). Thereafter, all interactions among significant variables were tested simultaneously. All significant interactions were included in the final model.

The model was built to address whether there is a differential survival among patients who received taxanes versus those who never receive taxanes as chemotherapeutic agents. This analysis was restricted to chemotherapy receivers. A categorical, time-dependent covariate was used for the first time use of taxane to account for time before receiving the therapy. The first time a treatment with a taxane was initiated, the covariate taxane is changed to $X(t)=1$, before it is $X(t)=0$. The time until this treatment was applied counts towards the no taxane period and the times after the treatment was initiated count towards the taxane group effect.

A multivariate Cox proportional-hazards model was constructed with age, race, metastatic site, ER status, HER-2 status, months to metastatic disease, and THE time-dependent taxane therapy indicator as predictive variables.

Due to the clinical importance of addressing the taxane impact on survival, taxane therapy indicator and age category (below 55 years and 55 years and older) were kept in the model even if they did not contribute significantly to the model. A backward stepwise process described above was employed to determine covariates that contribute significantly to the overall model. The initial model was:

$$\ln [h(t|x)/ h_0(t)] = \beta_T X_T(t) + \beta_{AgeCat} AgeCat + \Sigma \beta_i X_i \qquad \textbf{Eq. 2}$$

where $X_T(t)$ is an time-dependent covariate for taxane and β_T is the parameter estimate for the time-dependent variable, β_{AgeCat} the parameter estimate for the dichotomized age variable, and β_i's are the parameters for the fixed variables X_i's (i=1,2,…,5). In Table 5, $X_T(t)$ corresponded to the variable TaxUse, X_1 to White, X_2 to ERp, X_3 to Her2p, X_4 to Bone, and X_5 to the continuous variable MoMet.

3   RESULTS

Descriptive statistics and Kaplan-Meier survival curves for the univariate models are presented first, followed by the results from the multivariate model.

3.1   Descriptive Statistics

Subject socio-demographics and clinical characteristics are presented in Table 6. All patients were female, aged 28 to 90 years. The majority of subjects were white (92%), and about half of the patients were deceased (49%). Two hundred women were younger than 55 years at time of metastatic diagnosis and 176 were older.

Table 6. Socio-Demographic and Clinical Characteristic of Subjects

Variable	N	Percent	Mean	SD	Range
Gender					
Female	379	100	-	-	-
Race					
White	348	92	-	-	-
Non-White	31	8	-	-	-
Survival Status					
Deceased	187	49	-	-	-
Receptor Status					
ER positive	262	69	-	-	-
ER negative	113	30	-	-	-
HER-2 positive	127	34	-	-	-
HER-2 negative	198	52	-	-	-
Metastatic Location					
Bone	126	34	-	-	-
Bone and/or Visceral	233	62	-	-	-
Age			54.5	12.8	28–90
Young [years]	200	53	44.8	6.5	28–54
Old [years]	176	47	65.5	8.6	55–90
Diagnosis to Metastatic Disease [months]	372	98	45.5	54.2	0-459

Note: ER: estrogen receptor, HER-2: human epidermal growth factor 2;

Table 7. Number of Months on Sequential Therapy

Sequential Treatment Order	N	Mean	SD	Range
Treatment 1	375	8.6	10.5	1-86
Treatment 2	312	7.0	8.6	1-76
Treatment 3	236	6.7	8.7	1-73
Treatment 4	178	5.3	6.4	1-60
Treatment 5	129	4.8	6.5	1-60
Treatment 6	92	3.0	2.8	1-19
Treatment 7	55	4.2	4.8	1-24
Treatment 8	29	4.2	3.7	1-13
Treatment 9	22	3.8	3.7	1-15
Treatment 10	13	2.2	1.5	1-6
Treatment 11	8	3.4	2.2	1-7
Treatment 12	7	4.3	4.9	1-15
Treatment 13	2	1.5	0.7	1-2

About two thirds of study patients were estrogen receptor positive and about one third HER-2 receptor positive (Table 6). One third had metastases in the bone alone at the time of metastatic diagnosis. The mean time from the initial diagnosis of breast cancer to metastatic disease was 45.5 months, ranging from 0 to 41 years.

Table 7 summarizes treatment-related data, number of subjects on sequential therapy and mean time on each therapy in sequence. In this study, the maximum number of sequential treatments (number of treatment lines) received by the patient was 13. The mean number of months on each therapy in sequence showed a decreasing trend. Median survival times are summarized in Table 8. The median survival time from metastatic diagnosis was 30 months in all patients and 18 months in the deceased group.

Table 8. Mean Survival Times

Metastatic Survival [months]	N	Median (months)
All Patients	374	30
Age Group		
Young	200	32
Old	179	29
Race		
White	348	32
Non-White	31	18
Estrogen Receptor		
Positive	262	41
Negative	113	22
Her2 Receptor		
Positive	127	40
Negative	198	27
Metastatic Location		
Bone	126	33
Bone/Visceral	233	28
Till Metastatic Diagnosis		
Short (<30 months)	187	24
Long (≥30 months)	185	33
1st line Taxane*		
Yes	103	31
No	179	32

* among chemotherapy receivers

The median survival time for specific covariate categories are ranging from 18 to 41 months (Table 8). The median overall survival time from initial diagnosis of breast cancer was 48 months in the deceased patients, ranging from 1 to 25.2 years. Among the 282 chemotherapy receivers, the median survival times for t patients who received taxane as their first line therapy and those who did not were 31 months and 32 months, respectively.

3.2   Univariate Survival Models

Kaplan-Meier Curve

All Patients

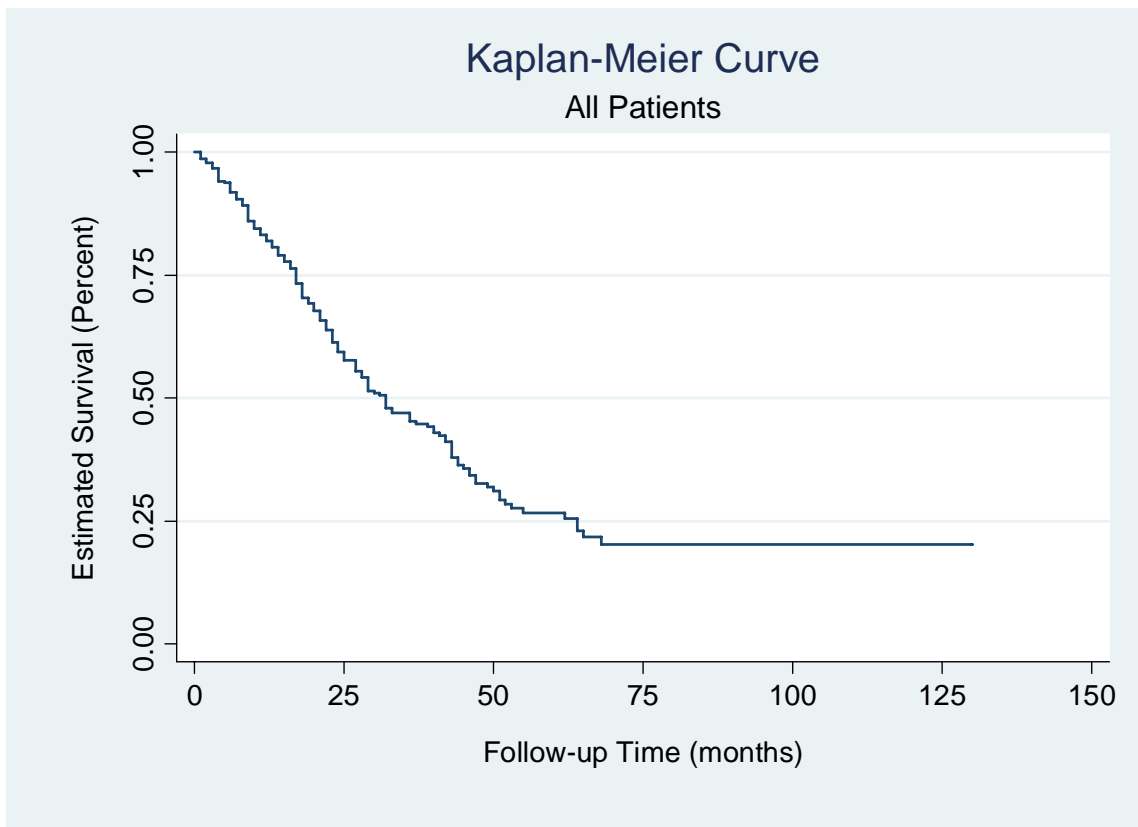*Estimated Survival (Percent)* vs *Follow-up Time (months)*

Figure 1. Kaplan-Meier survival curve for all patients

Figure 1 presents a univariate Kaplan-Meier curve of survival for all patients. There is a steady decrease in survival over time. The median survival was 30 months and after 65 months no deaths were observed.
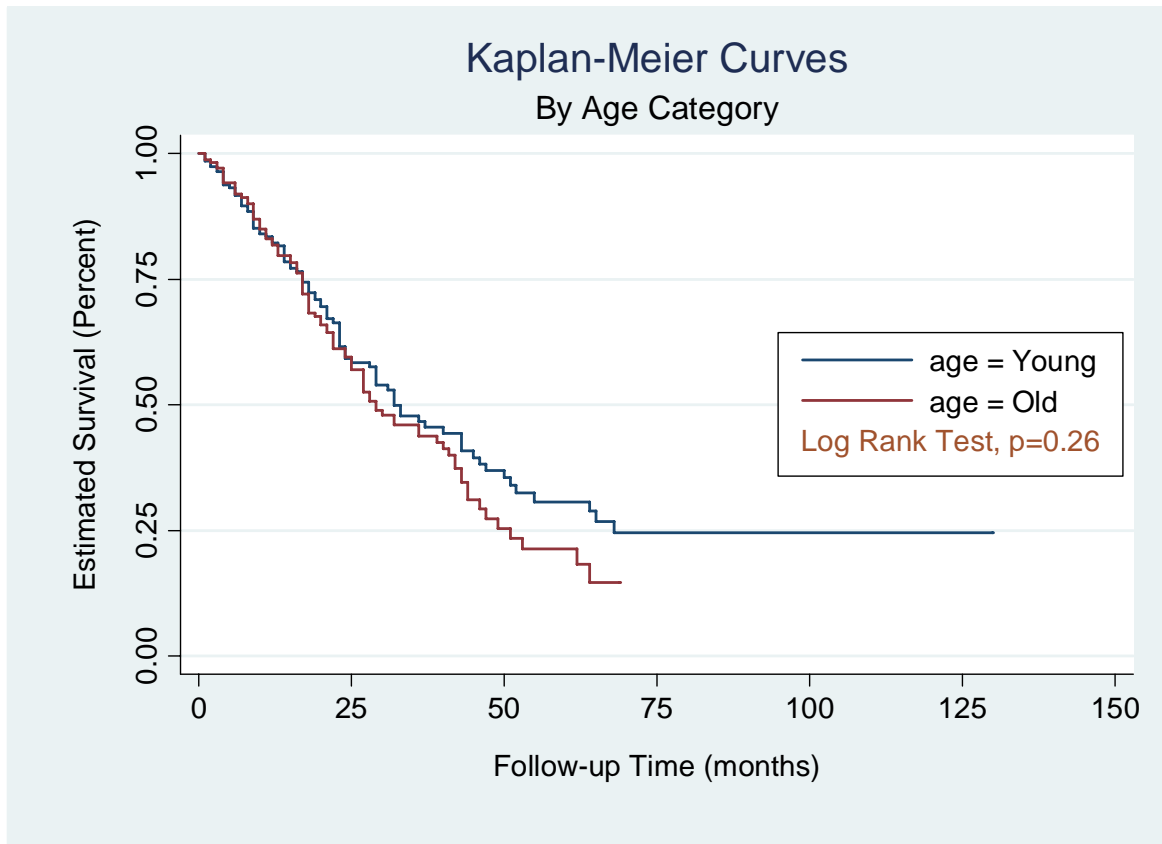
Figure 2. Kaplan-Meier survival curve for all patients by age category

Table 9 shows the log-rank test results for differences among the strata for each covariate. Figure 2 presents the univariate Kaplan-Meier curves for the dichotomized covariate age. The median survival was 32 months and 29 months for young and old patients, respectively. The curves for patients aged below 55 years and those 55 years and older did not differ significantly.

Table 9. Log Rank Test for differences between Kaplan-Meier Curves and Link Test

Variable	β	SE	χ^2	p-value
Log Rank Test				
Age	-	-	1.28	0.26
Race	-	-	9.57	0.002
ER	-	-	14.60	0.0001
Her2	-	-	1.68	0.19
Metastatic Location	-	-	0.76	0.38
Metastases Development Time	-	-	1.65	0.20
1st Line Taxane Therapy*	-	-	0.27	0.61
*Link Test**				
MoMet	-0.0024	0.002	1.93	0.17
MoMet$^{\Delta}$	0.0007	0.005	0.02	0.88
MoMet2$^{\Delta\Delta}$	0.0001	0.00003	0.30	0.58

Note: * among chemotherapy receivers, $^{\Delta}$ with MoMet2 in the model, MoMet2=(MoMet)^2, $^{\Delta\Delta}$ with MoMet in the model
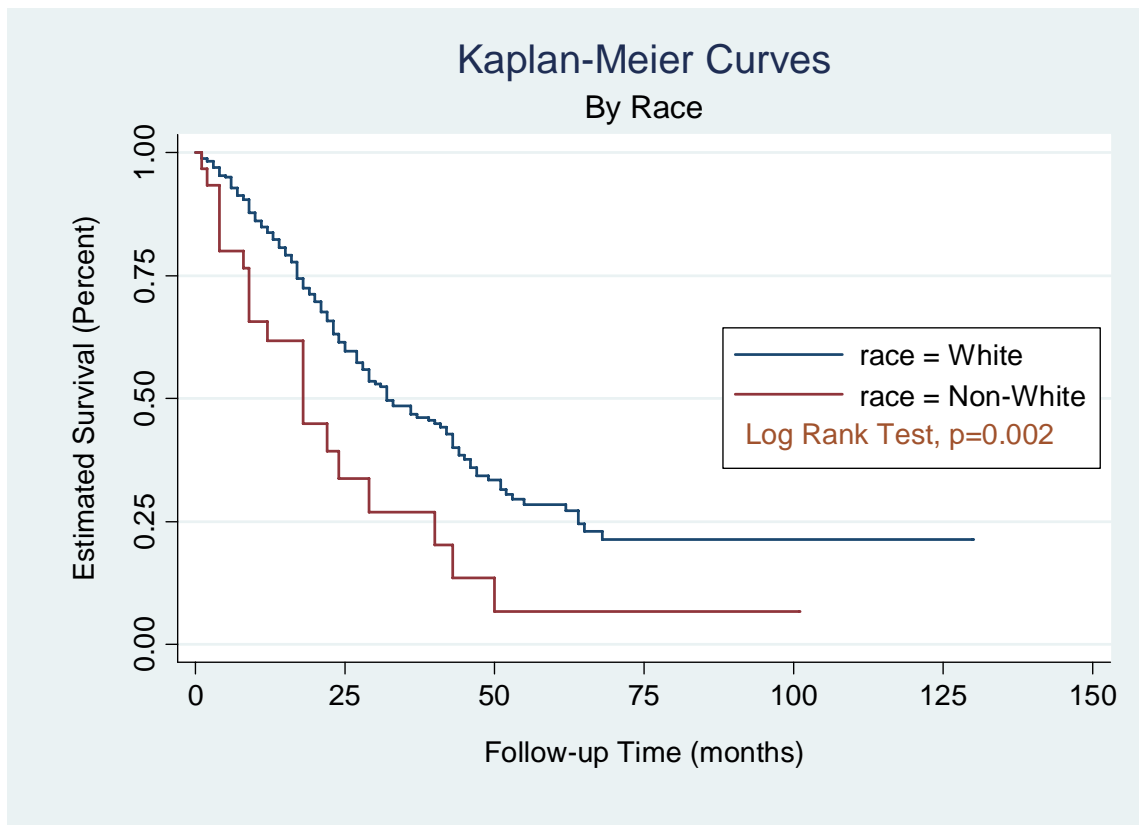

Figure 3. Kaplan-Meier survival curve for all patients by race

Figure 3 shows the univariate Kaplan-Meier curves for the covariate race. The median survival was 32 months and 18 months for white and non-white patients, respectively. The curves for white patients and non-white patients differed statistically significantly, with white having a better survival.

Figure 4. Kaplan-Meier survival curve for all patients by estrogen receptor type

Figure 4 shows the univariate Kaplan-Meier curves for the covariate estrogen receptor type. The curves for positive and negative estrogen receptors differed highly significantly; patients who had cancer with positive estrogen receptors were surviving longer. The median survival was 41 months and 22 months for women with positive and negative estrogen receptor, respectively.

Figure 5 shows the univariate Kaplan-Meier curves for the covariate HER-2 receptor type. The median survival was 40 months and 27 months for women with positive and negative HER-2 receptor, respectively. The curves for positive and negative HER-2 receptors cross each other twice and do not differ significantly.

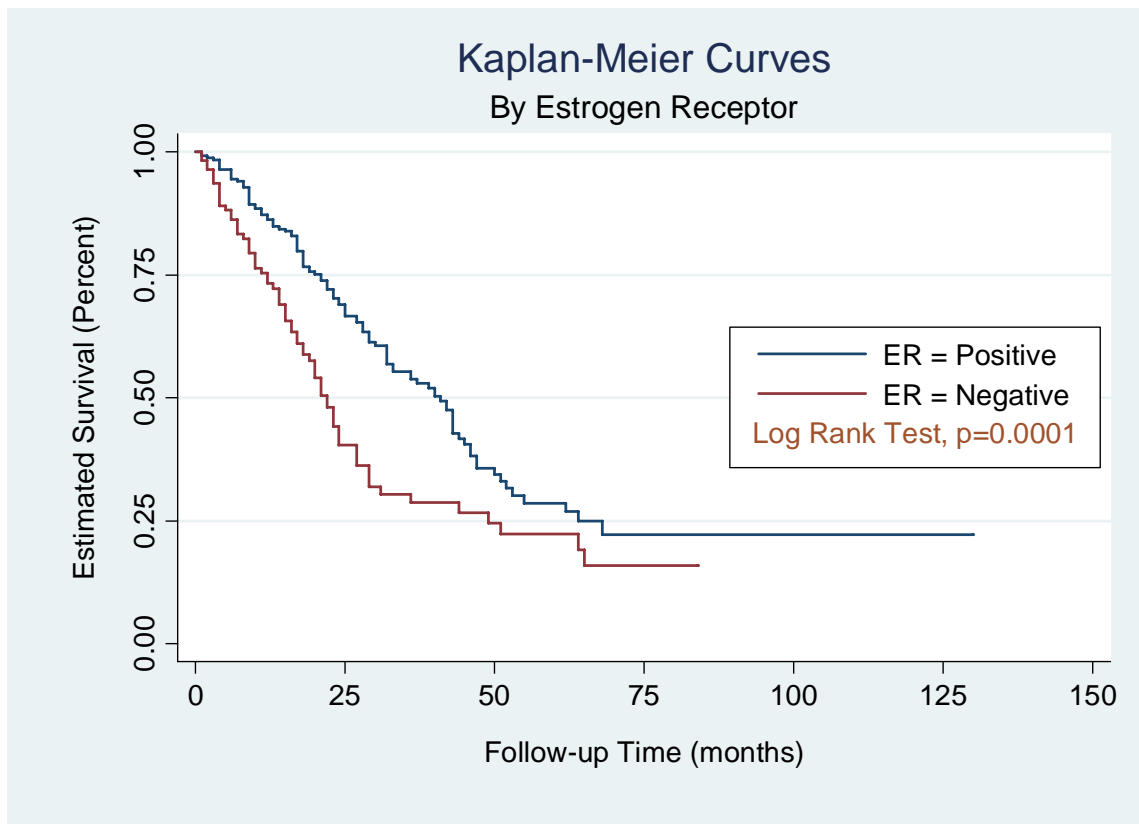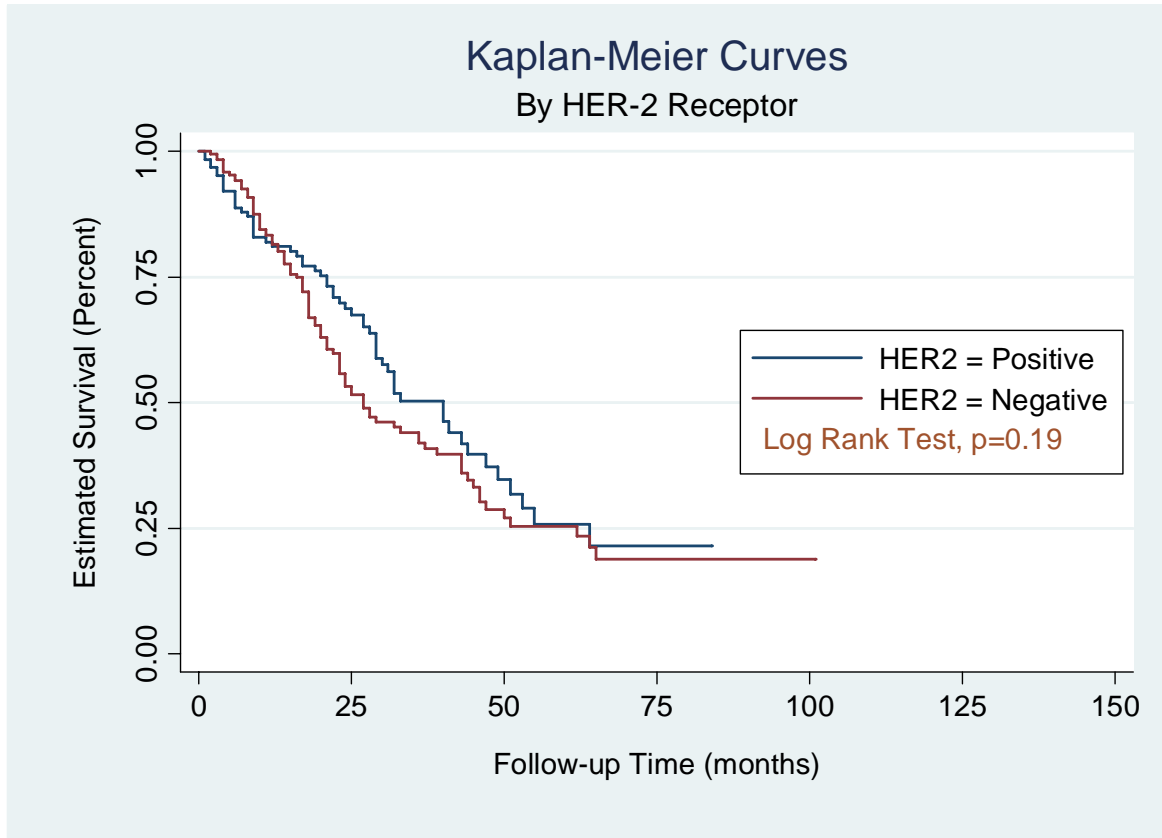**Figure 5.** Kaplan-Meier survival curve for all patients by HER-2 receptor

Figure 6 shows the univariate Kaplan-Meier curve for the covariate metastatic location. The curves for bone versus bone and/or visceral did not differ. The median survival was 33 months and 28 months for women with metastases in bone and bone and/or visceral organs, respectively.
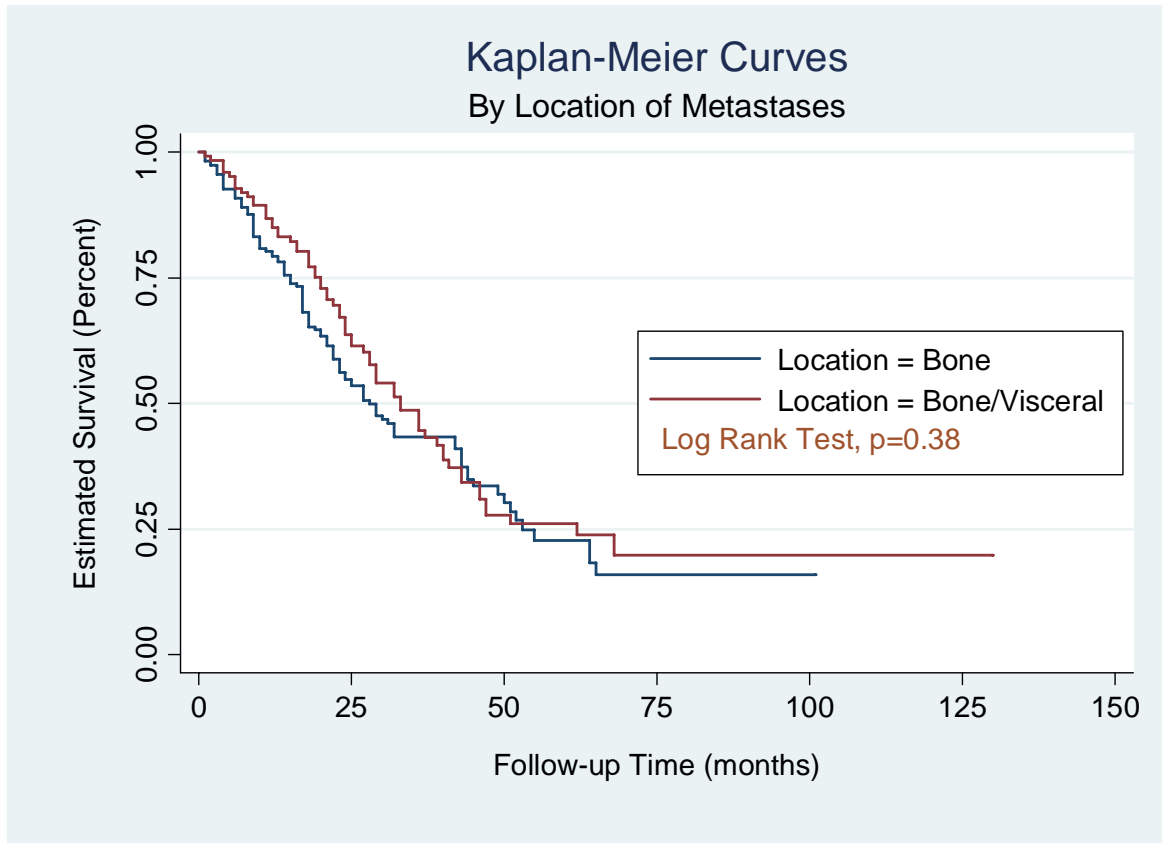
Figure 6. Kaplan-Meier survival curve for all patients by metastatic location

The covariate MoMet, months to diagnosis of metastatic disease from initial diagnosis of breast cancer, was analyzed in the dichotomized form (MoCat) and in its continuous form. Figure 7 shows the univariate Kaplan-Meier curve for the dichotomized covariate time to metastatic disease. The median survival was 33 months and 28 months for women less than 30 months from initial diagnosis to metastatic disease and 30 months and more, respectively. The curves for shorter than 30 months time to metastatic disease compared to 30 months and more did not differ. The continuous variable MoMet was evaluated using a goodness of fit test. Table 9 shows that the influence of the quadratic term was not significant.
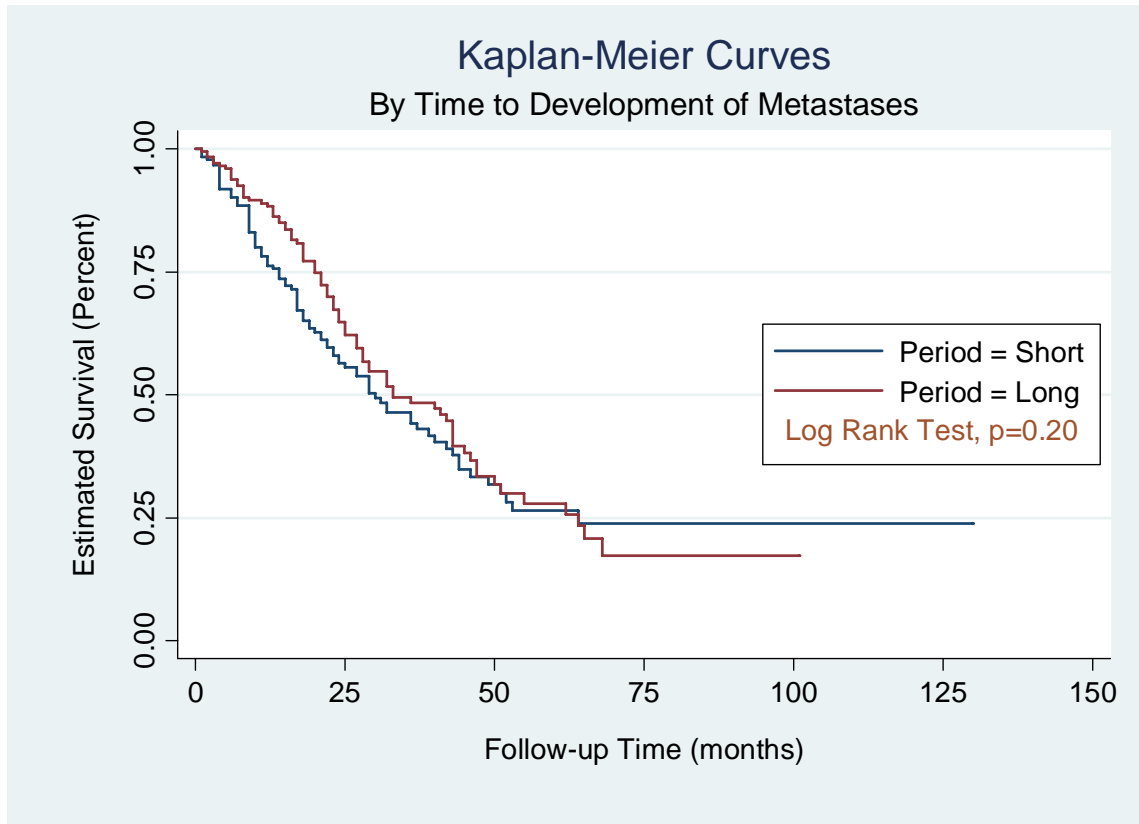
Figure 7. Kaplan-Meier survival curve for all patients by time to diagnosis

Figure 8 shows the univariate Kaplan-Meier curve for the covariate 1st line taxane. The curves for 1st line taxane to no taxane in 1st line therapy did not differ. The median survival was 31 months and 32 months for women who received first line taxane therapy and those who did not, respectively.

For all univariate models, proportionality assumption were met for all covariates based on the plots of –ln(–ln(Survival probability)) versus ln(follow-up time). Plots are presented for taxane use as first line therapy in Figure 9 and for all other fixed covariates in Figure 10.

Figure 8. Kaplan-Meier survival curve for all patients by first line therapy
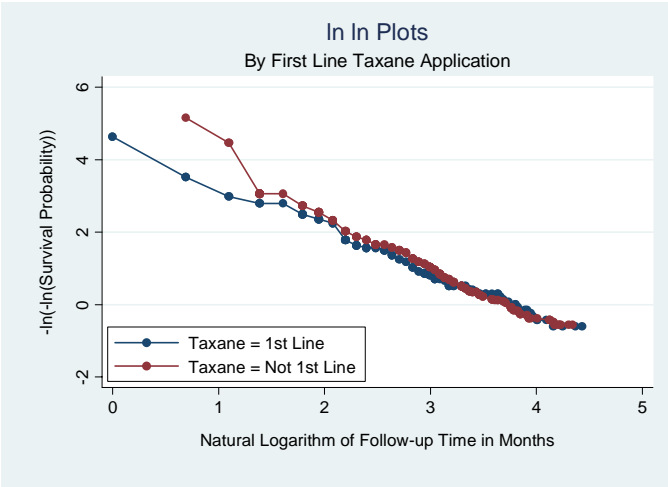
Figure 9. Graphical proportionality assumption test for first line therapy
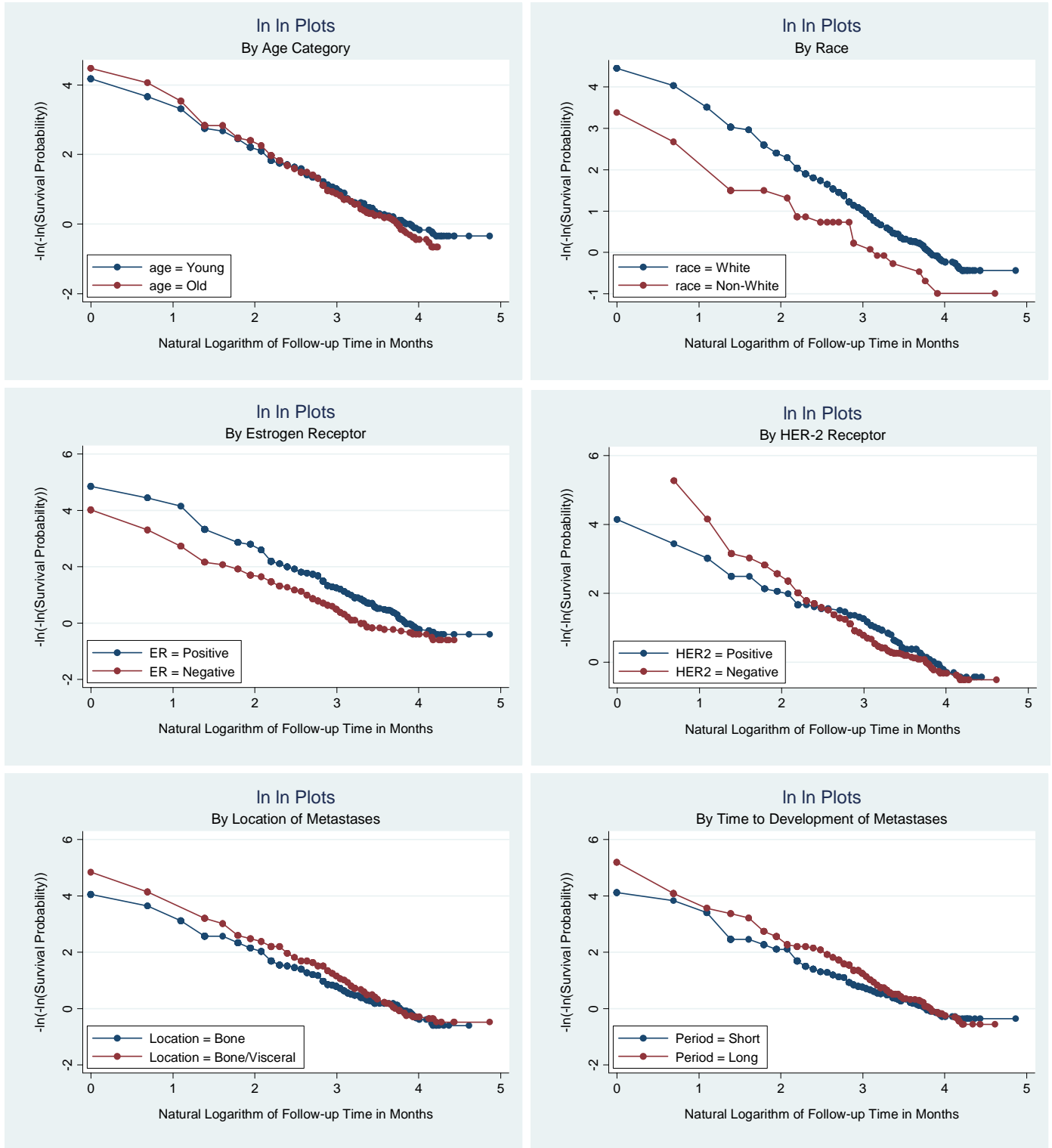
Figure 10. Graphical proportionality assumption test for fixed covariates

To summarize, significant differential effect on survival was observed for race, with white patients showing a better survival and estrogen receptor, with women who had positive receptor cancer having better survival. No difference in survival was found for other covariates and taxane-containing regimens versus no taxane as first line therapy.
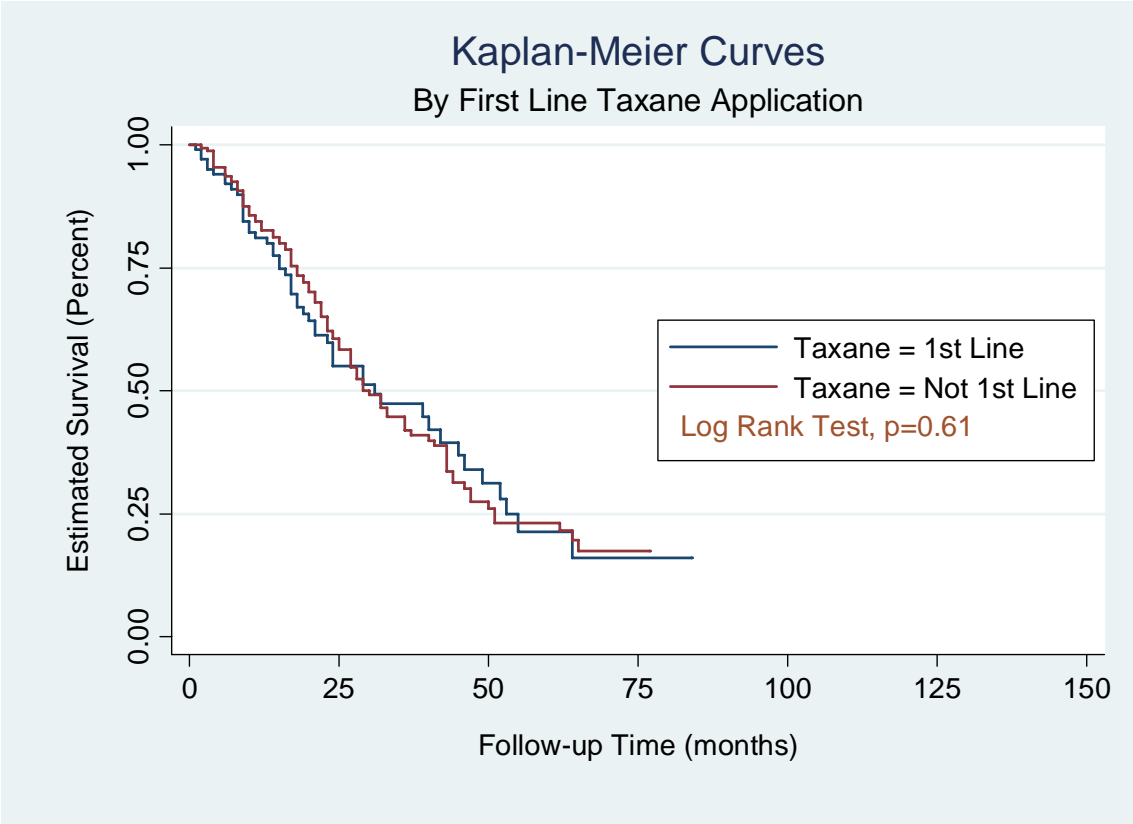
3.3 Multivariate Survival Model

The number of contributions for taxane as a time-dependent variable is presented in Table 10. Among chemotherapy receivers about half of the records contributed to the taxane use category.

Table 10. Time-Dependent Taxane Therapy Among Chemotherapy Receivers

Taxane Treatment	N	Percent
Total	384	100
Taxane Use	204	53
No Taxan Use	180	47

The final model to compare taxane versus no taxane resulted in

$$\ln [h(t|x)/h_0(t)] = \beta_T\, X_T(t) + \beta_{AgeCat}\, AgeCat + \beta_{White}\, White + \beta_{ERp}\, ERp + \beta_{ERp}\, HERp \qquad \textbf{Eq. 3}$$

based on the backward selection method. After including significant covariate interactions, the final model yielded the following estimates (Table 11).

Table 11. Model Parameter Estimates

Variable	β	SE	χ^2	p-value
Taxane Use	-0.09	0.30	0.09	0.76
Age Group	0.01	0.18	0.01	0.94
Race	-0.28	0.39	0.55	0.46
ER	-1.64	0.34	22.70	<.0001
HER-2	0.11	0.60	0.03	0.86
Interaction between Taxane and ER	0.76	0.39	3.86	0.05
Interaction between Race and HER-2	-1.24	0.58	4.54	0.03
Interaction between ER and HER-2	1.03	0.37	7.88	0.01

For assessing the proportional hazard assumption for the multivariate model, the interactions of the covariate with time in the natural logarithm scale were included in the model. The global test of proportionality based on the model including time-covariate interactions was not significant with $\chi^2=11.11$, p=0.20 with 8 degrees of freedom. The proportionality assumption for the model was acceptable because the global test was not significant. Table 12 presented the hazard ratios and confidence intervals for all patients corresponding to the parameter estimates in Table 11.

Table 12. Model - Hazard Ratios

Variable	All Patients		Without Unusual Point	
	Hazard Ratio	CI	Hazard Ratio	CI
Taxane Use	0.91	(0.51, 1.65)	0.82	(0.46, 1.48)
Age Group	1.01	(0.71, 1.44)	0.96	(0.67, 1.37)
Race	0.76	(0.35, 1.62)	0.82	(0.38, 1.76)
ER	0.19	(0.10, 0.38)	0.15	(0.08, 0.30)
HER-2	1.12	(0.34, 3.62)	1.07	(0.33, 3.47)
Interaction between Taxane and ER	2.14	(1.00, 4.59)	2.34	(1.09, 5.03)
Interaction between Race and HER-2	0.29	(0.09, 0.90)	0.26	(0.08, 0.81)
Interaction between ER and HER-2	2.80	(1.36, 5.78)	3.31	(1.60, 6.84)

Note: CI: confidence interval

One potentially influential point (observation 323) was observed in Figure 11. After reviewing the data set, it was apparent that this record belonged to a 44-year-old white woman. This patient had a cancer with negative estrogen and HER-2 receptors. During the course of treatment she received taxanes after 36 months during her third sequential therapy and died after 65 months from metastatic diagnosis. None of the values were unusual.

To investigate the impact of this point on the inferences of the model, the final model was fitted to all data after excluding this data point. Table 12 presented the hazard ratios and confidence intervals for data from all patients without the influential point. Inferences did not change and the associated hazard ratio changed minimally. Therefore the data record was kept in the final model.
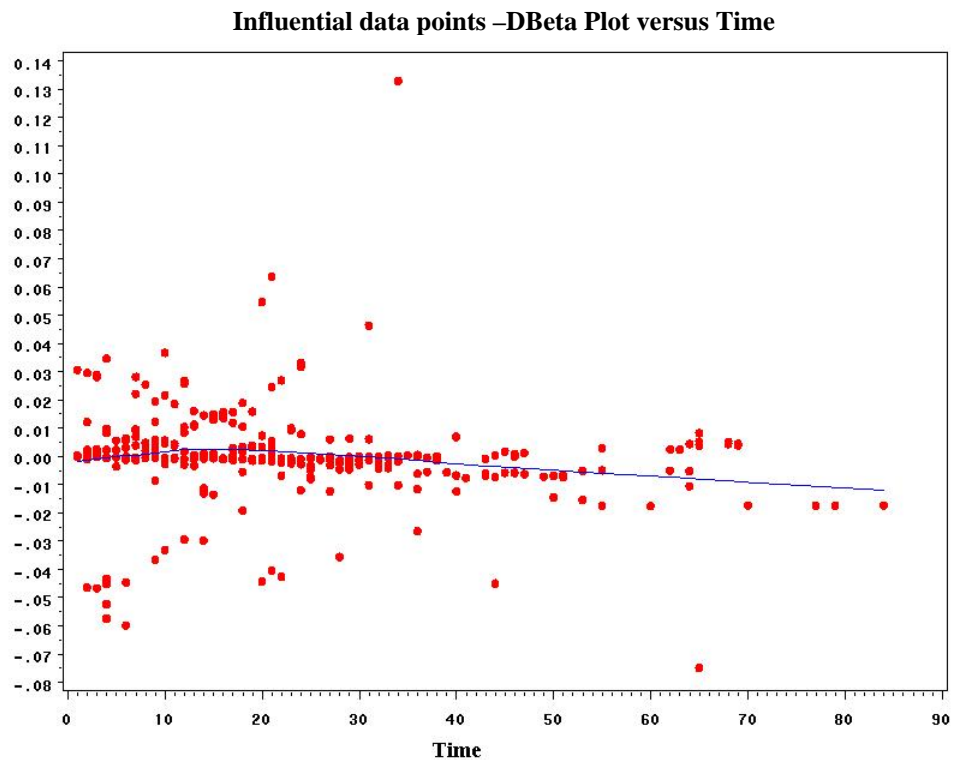
Influential data points –DBeta Plot versus Time

Figure 11. Dbeta Plot for evaluating influential data points

To understand the change in hazard ratio compared to the baseline (a hazard ratio of 1), percent change or a multiplication factor were computed. Logically, percent change is zero, when the hazard ratio is equal to one. The calculation of percent change depended on whether the hazard ratio was smaller or greater than one. For hazard ratios greater than one but smaller than two, the decimal points behind the comma represent the percept change. For example, HER-2 showed a hazard ratio of 1.12 (Table 12), therefore the percent change was 0.12 that is 12%. For hazard ratios smaller than one, the percent change can be computed by inverting the hazard ratio. After the inversion, the same method to compute percent change applied as for hazard ratios greater than one. For example, the hazard ratio of taxane use was 0.91. The inverted hazard ratio was 1.10 that is 1 divided by 0.91, with a percent change of 10%. In case the hazard ratio or inverted hazard ratio was larger than two, a multiplication factor is presented instead of percent change. For example, for women with positive estrogen receptor the hazard ratio was 0.19. Inverted, this corresponded to 5.3, which is the multiplication factor. In the following, results for all main effects in Table 12 were related to these measures.

Taxane use reduced the hazard ratio by 10 percent and indicates a small protective effect on survival. Older age increases the hazard ratio minimally (1%). White race was a protective factor with a 32% reduction in hazard ratio. Nevertheless, all these contributions were not statistically significant. The only significant main factor was estrogen receptor; having a positive receptor cancer reduced the hazard ratio 5.3 times. Positive HER-2 receptor cancer was a negative factor with a 12% increase in risk of dying. The major factors in the model are the three interactions between taxane use and estrogen receptors, race and HER-2 receptors, and estrogen and HER-2 receptors.

For all the combination of covariates values, Table 13 presents the hazard ratios in relation to the baseline. The baseline corresponded to all covariate values set to zero, which represents a young non-white woman with negative estrogen and HER-2 receptors who did not receive taxane-containing regimens during the course of her treatment.

Table 13. Model – Hazard Ratios based on Combination of Covariate Characteristics

Taxane Use	Old Age	White	ER	HER-2	ΣβiXi	Hazard Ratio
1	1	1	1	1	-1.34	0.26
1	1	1	1	0	-1.24	0.29
1	1	1	0	1	-1.49	0.23
1	1	1	0	0	-0.36	0.70
1	1	0	1	1	0.18	1.20
1	1	0	1	0	-0.96	0.38
1	1	0	0	1	0.03	1.03
1	1	0	0	0	-0.08	0.92
1	0	1	1	1	-1.35	0.26
1	0	1	1	0	-1.25	0.29
1	0	1	0	1	-1.50	0.22
1	0	1	0	0	-0.37	0.69
1	0	0	1	1	0.17	1.19
1	0	0	1	0	-0.97	0.38
1	0	0	0	1	0.02	1.02
1	0	0	0	0	-0.09	0.91
0	1	1	1	1	-2.01	0.13
0	1	1	1	0	-1.91	0.15
0	1	1	0	1	-1.40	0.25
0	1	1	0	0	-0.27	0.76
0	1	0	1	1	0.49	0.61
0	1	0	1	0	-1.63	0.20
0	1	0	0	1	0.12	1.13
0	1	0	0	0	0.01	1.01
0	0	1	1	1	-2.02	0.13
0	0	1	1	0	-1.92	0.15
0	0	1	0	1	-1.41	0.24
0	0	1	0	0	-0.28	0.76
0	0	0	1	1	-0.50	0.61
0	0	0	1	0	-1.64	0.19
0	0	0	0	1	0.11	1.12

Estrogen receptor type was the only essential covariate when comparing taxane versus no taxane use in women with the same covariate patterns (Figure 12). Taxane-containing regiments were 9% beneficial for any women any age when her estrogen receptor was negative. Conversely, taxanes were not protective, even harmful with a 95% increase in risk of dying, to women with positive estrogen receptor cancer.
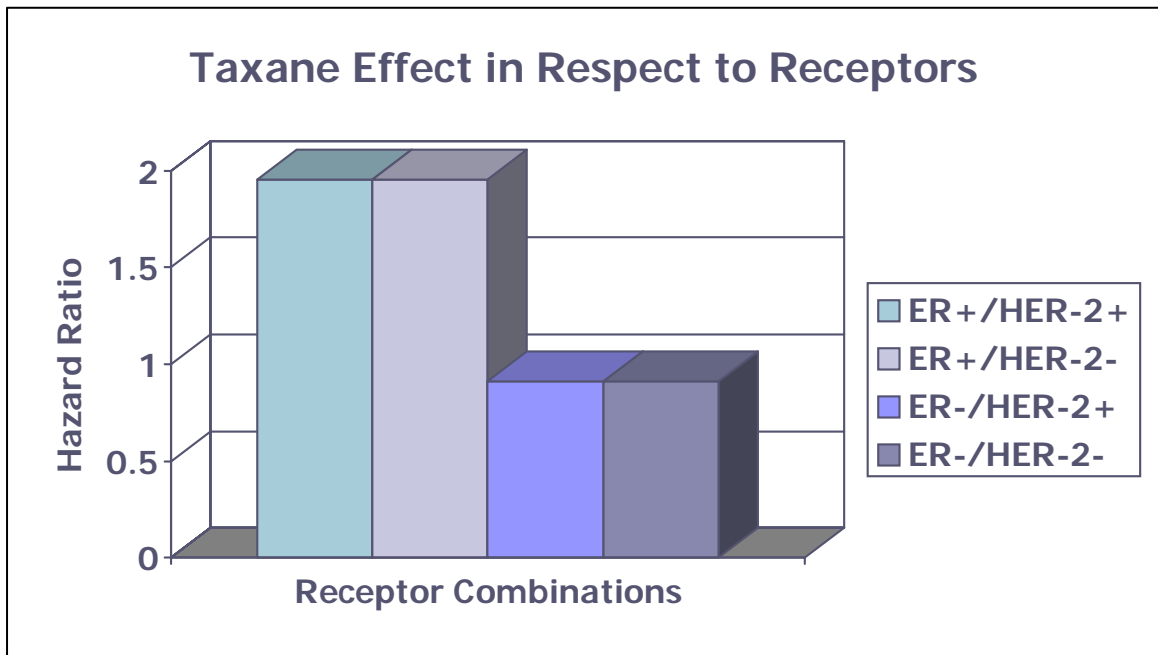
Figure 12. Taxane effect in respect of estrogen and HER-2 receptors

Age increased the risk of dying up to about 15% in women with negative estrogen receptor type irrespective of treatment. Among taxane user white women who had a positive HER-2 receptor cancer compared to negative HER-2 receptor cancer had a 2.3 and 1.8 decreased hazard for positive and negative estrogen receptor type, respectively. This strongly reduces their risk of dying. Estrogen positive women who had a positive HER-2 receptor type had a 6.2 fold increased hazard ratio compared to estrogen receptor negative patients with a positive HER-2 receptor type.

4   DISCUSSION

This study is an essential part of clinical research on evaluating taxane therapy in the sequential treatment course of metastatic breast cancer patients. Since due to ethical issues no clinical trial will ever be conducted addressing such a question, this observational study is a very useful way to obtaining more insight in the management of metastatic breast cancer and the relative effectiveness of these therapeutic agents.

Taxane-containing regimens administered as a first line therapy did not result in a better survival. This corresponds to the findings in the clinical trial review of Bernhard-Matry et al. (2003). The real effect of these agents emerged in the analysis of sequential taxane use. The benefit of taxanes over no taxanes among chemotherapy receivers depended strongly on the receptor of the cancer. Women with negative estrogen receptor cancer profited the most from taxane-conatining regiments. An increased risk of dying was observed in women with positive estrogen receptor cancer. This may be due to an imbalance in benefit to toxic side effects ratio, which in this subpopulation may be more in favor of the side effects. Other factors may contribute to this effect, such as the tendency to administration taxanes in estrogen positive women at a later time during their sequential treatment course or differences in patient characteristics (e.g., location of metastases). Further investigations are needed to fully understand this effect.

HER-2 overexpression increased the risk of dying. The effect of its interaction with race and estrogen receptor type valuably added to the understanding of this factor in the management of metastatic breast cancer in that having the combination of positive HER-2 receptor and negative estrogen receptor cancer compared to a cancer with both receptors being negative enormously reduced the risk.

Although age is an important factor in the etiology of breast cancer, it played a minor role in the analysis of sequential taxane therapies. Similarly, the time till development of metastases and their location did not contribute to the understanding of the effect of taxane use in the sequential therapy setting.

Since there are no standard guidelines in the use of taxane in metastatic breast cancer, the routine clinical use of the taxanes is highly dependent on physicians' bias towards weighing their benefits and risks. The current study adds significantly to the understanding of sequential therapy and the impact of taxane-containing regimens in the treatment course. The findings are useful to guide clinicians in their decision-making regarding therapeutic regimes for metastatic breast cancer. Therefore, this provides physicians and health care professionals with an essential tool to improve public health.

APPENDIX

Data Set Description

All data described below are from a database. Table A - 1 presents the coding for fixed variables (from Table 4). For time-dependent variables, treatment coding is presented in Table A - 2 for the overall treatment category (Tx#), in Table A - 3 for chemotherapies (Tx#Chemo), in Table A - 4 for hormonal therapies (Tx#Horm), and in Table A - 5 for response (Tx#Resp) and performance status (Tx#PS).

Table A - 1. Data Set –Variables Codes

Variables	Code	Description
ID_pat	1-363	integer from 1
Age	28-90	integer from 18
Race	1	White
	2	African American
	3	Asian
	4	Other
ER	1	positive
	2	negative
	3	unknown
Her2	1	positive
	2	negative
	3	unknown
LocMet	1	bone
	2	bone and/or visceral organ
Sites	1-8	integer from 1
MoMet	0-459	integer from 0
Msurv	1-129	integer from 0
Bcsurv	1-302	integer from 0

Note: Missing values are coded –1.

Table A - 2. Data Set – Overall Treatment Category Codes

Tx#	Description
1	No Active Therapy, Observation Only
2	Chemotherapy
3	Chemotherapy + Herceptin
4	Herceptin Alone
5	Hormonal Therapy Alone
6	Hormonal Therapy + Chemotherapy
7	Hormonal Therapy + Chemotherapy + Herceptin
8	Immunologic Therapy
9	Hormonal Therapy + Herceptin
10	Vaccine + Chemotherapy
11	Vaccine + Hormonal Therapy
12	Vaccine alone
13	Biologic Therapy + Herceptin

Note: Missing values are coded −1.

Table A - 3. Data Set – Chemotherapy and Hormonal Therapy Codes

Tx#Chemo	Description
1	Adriamycin
2	Cytoxan
3	5-FU
4	Methotrexate
5	Navelbine
6	Xeloda
7	Taxol
8	Taxotere
9	Mitoxantrone
10	Gemzar
11	Carboplatin
12	Epirubicin
13	Doxil
14	Veg F.
15	Theraptope
16	Leukovorin
17	Epitholone B
18	Cisplatin
19	Carboplatin/Taxol
20	Taxotere/Xeloda
21	Carbo/Taxotere
22	Adriamycin/Cytoxan
23	Taxotere/Gemzar
24	Adriamycin/Taxotere/Cytoxan
25	Same as Code 19
26	Cytoxan/Methotrexate/5-FU
27	5-FU/Epirubicin/Cytoxan
28	Epitholone/Xeloda
29	Adriamycin/Taxotere
30	Abraxane
31	Gemzar/Taxotere
32	5-FU/Mitoxantrone/Leucovorin
33	Xeloda/Mitoxantrone
34	Cytoxan/Epirubicin
35	Taxotere/Epirubicin
36	CAF
37	Temodur
38	Xeloda/Veg F.
39	Cisplatin/Gemzar

Note: 38 chemotherapies due to same coding of 19 and 25; Missing values are coded –1.

Table A - 4. Data Set – Hormonal Therapy Codes

Tx#Horm	Description
1	Tamoxifen
2	Femera
3	Megace
4	Arimidex
5	Lupron
6	Aromasin
7	Zoladex
8	Raloxifine
9	Faslodex
10	Fareston
11	Fulvestrant
12	Lupron/Femera
13	Arimidex/Femera
14	Arimidex/Lupron
15	Aromasin/Faslodex
16	Faslodex/Tamoxifen
17	Arimidex/Faslodex
18	Lupron/Tasmoxifen
19	Lupron/Faslodex
20	Lupron/Aromasin
21	Faslodex/Femera
22	Tamoxifen/Lupron/Megace
23	Tamoxifen/Megace
24	Faslodex/Aromasin
25	Arimidex/Aromasin
26	Megace/Arimidex
27	Megace/Aromasin
28	Megace/Lupron
29	Lupron/Faslodex/Megace
30	Fareston/Zoladex
31	Femera/Zoladex
32	Arimidex/Zoladex
33	Megace/Zoladex
34	Tamoxifen/Aromasin
35	Megace/Faslodex
36	Faslodex/Femera/Megace

Note: Missing values are coded –1.

Table A - 5. Data Set – Response and Performance Status Codes

Treatment Code	Description
Response (Tx#Resp)	
1	improved
2	stable
3	worse
Performance Status (Tx#PS)	
1	good (0-1)
2	poor (>1)

Note: Missing values are coded –1.

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