Albert Liao
MSCR Graduation Thesis: Assessing Predictors and Outcomes of Guideline-Concordant Treatment in Women with Early Stage Breast Cancer

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AB, Princeton University, 2012

Clinical Research

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Assessing Predictors and Outcomes of Guidelines-Concordant Treatment in Women with Early Stage Breast Cancer

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An abstract of a thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of

Master of Science

In Clinical Research

2018

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Introduction:

Previous studies examining disparities in treatment guideline adherence in early-stage breast cancer have been limited by small study sample sizes, localized geography, unknown causal factors, and lack of diverse populations. To address these issues, we used the National Cancer Data Base to assess socioeconomic, clinical, and facility factors that impact treatment compliance with the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines.

Methods:

The NCDB file contains 2,246,280 patients diagnosed between January 1st, 2004 to December 31st, 2014. Chi-square tests were used to identify significant differences in rates of guidelines adherence over time for facility type, facility location, quartiles of income, education, insurance status, distance, and tumor staging. Logistic regression modeling was used to compute odds ratios for likelihood of guidelines adherence controlling for these factors. A backward multivariable Cox proportional hazard model was fit and an extended Kaplan-Meier curve plotted. Overall survival was measured in months from date of diagnosis to date of either death or last follow-up.

Results:

Multivariate models revealed decreased use of post-breast conserving surgery (BCS) radiation, chemotherapy, and immunotherapy for women ≥ 75; for lower-volume treatment centers; for patients without private insurance; for patients in the lowest income quartiles; for patients in the lowest education quartile; for patients with higher comorbidities; and for patients having unknown stage tumor. Treatment compliance led to overall mortality reductions for all treatments examined.

Conclusion:

Certain socioeconomic, clinical, and facility factors influence guideline-concordant care and subsequent outcomes for patients with early-stage breast cancer. Approaches to reducing disparities in breast cancer treatment have had mixed progress; this points to a need for tailored interventions to improve guideline compliance so that non-compliance can be prevented in at-risk populations. With the new emphasis on value-based care, it is important to address these discrepancies in treatment and thus enhance survival for all individuals through better adherence to guideline concordant therapy.

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Albert Liao

MSCR Graduation Thesis: Assessing Predictors and Outcomes of Guideline-Concordant Treatment in Women with Early Stage Breast Cancer

Introduction

Epidemiology

Breast cancer is the most commonly diagnosed cancer worldwide, accounting for more than 1.8 million cases annually [1]. About 12% of women (1 in 8) will be diagnosed with breast cancer in her lifetime. It remains the most commonly diagnosed female cancer, and the second most common cause of cancer death among women [2]. In the United States, there are approximately 3 million women who are living with breast cancer [2], with more than 249,000 new cases diagnosed per year. Nationally, the disease will account for over 40,000 deaths annually. During the 1980s and 1990s, breast cancer incidence rose sharply, from 102.3 cases per 100,000 patients in 1980 to 141.5 cases per 100,000 patients in 1999 [3]. The causes of this increase were multifocal. Increased awareness of screening protocols and more sensitive mammography equipment resulted in earlier diagnoses [4]. In addition, the widespread use of hormone replacement therapy in certain groups led to an increased risk of breast cancer in the overall population [5]. Finally, increased obesity rates in Americans led to a rise in incidence for many malignancies, including breast cancer [6]. After decades of increasing incidence rates secondary to earlier, more sensitive detection methods, use of post-menopausal hormone replacement therapy (HRT), and increasing obesity rates, breast cancer incidence finally stabilized and, in some cases, even decreased after 2002 in the United States. The incidence rates decreased from 1999 to 2007 by an average of 1.8 percent per year [7].

While breast cancer incidence rates have traditionally been higher in Caucasians compared to African-Americans, these differences have converged over the recent years. According to the Surveillance, Epidemiology, and End Results (SEER) database from 2008 to 2012, breast cancer incidence rate was highest in non-Hispanic whites at 128.1 per 100,000 patients, while the incidence in non-Hispanic black patients lagged only slightly behind, at 124.3 per 100,000. However, the mortality rate was nearly 42% higher in non-Hispanic black patients compared to Caucasian patients [8]. Among

women younger than 40 years in the United States, the rates of invasive breast cancer are higher in black women compared to white women; among women 40 years or older, the incidence rates are higher in the Caucasians compared to black patients. This "black-white crossover" in breast cancer incidence was identified several decades ago and continues to be a source of discussion of cancer epidemiology and biological differences between varied populations [9]. African-Americans women are more often diagnosed with late stage breast cancer than other ethnicities and races [10]. They are also more likely to develop more aggressive forms of the cancer, such as triple negative (estrogen/progesterone/HER2 negative) breast cancer, whereas white women had higher rates of hormone receptor positive/HER2 negative breast cancer [7, 9]. Incidence rates in Alaska Native/American Indians (91.9 per 100,000 females), Asian/Pacific Islanders (88.3 per 100,000 females), and ethnic Hispanics (91.9 per 100,000 females) were also significantly lower compared to non-Hispanic blacks. These lower numbers are thought to be due to differences in inherent breast cancer risk factors [8].

While breast cancer is one of the most widely diagnosed cancers, overall deaths secondary to this disease have been steadily decreasing for decades. The average five-year survival rate for patients with newly diagnosed breast cancer is 89%, the 10-year rate is 83%, and the 15-year rate is 78% [11]. These rates reflect the advances made in breast cancer detection and adjuvant therapy over the last decades. The United States Preventive Services Task Force (USPSTF) currently recommends biennial screening mammography for women aged 50 to 74 years [12]. This is because the sensitivity and specificity of diagnostic mammograms decline with breast density and younger age. Patients younger than age 50 who place higher value on earlier diagnosis compared to potential harms may begin screenings from age 40-49. Currently in the United States, over 90% of breast cancers are identified mammographically, with just 10% being detected through physical exam [13]. Patients who present with

suspicious new masses should receive a diagnostic mammogram instead of a screening mammogram due to greater sensitivity and lower specificity [14].

Increased precision and sensitivity in instruments mean that patients are being diagnosed with small tumor disease that would have been read as (false) negative by past machines. More than 80% of breast cancer patients from 2004 to 2011 were diagnosed in either stage I or stage II [10]. Patients whose cancers are confined to breast tissue have a relative five-year survival rate of 99% (stage 0 to I), while patients whose cancer has spread to regional lymph nodes (stage II) have a five-year survival rate of 85%. Metastatic, or stage IV, breast cancer patients who received surgery had a five- year survival rate of about 22% and a 10-year survival rate of 9.6% [15].

Breast Cancer Staging

The first Tumor Node Metastasis (TNM) staging for breast cancer was published in 1960 by the American Joint Committee on Cancer Staging (AJCC). The latest edition, the 7th edition, was released in 2009. The purpose of the staging criteria is to group patients into categories that will both determine the proper treatment (prediction of response) and the overall prognosis. According to the AJCC, T staging is defined by size:

1. T0: No evidence of primary tumor
2. Tis: Carcinoma in situ, further divided into DCIS, LCIS, and Paget's disease
3. T1: Tumor that is 2 cm or less in greatest dimension, with further division into T1a (.1cm>tumor>1cm), T1b (.5cm>tumor>1cm), T1c (1cm>tumor>2cm)
4. T2: Tumor that is between 2 cm to 5 cm
5. T3: Tumor that is greater than 5 cm

6. T4: Tumor of any size that has extended directly into the chest wall or skin (dermis invasion alone does not qualify). T4 is further divided into T4a: extension to chest wall excluding pectoralis muscle, T4b: edema, T4c (a and b combined), T4D: inflammatory carcinoma

Lymph node (N) classification is defined according to the method of diagnosis: clinical or pathological. Clinical diagnosis refers to staging performed using physical examination. Pathological staging incorporates clinical staging results with additional data from surgical exploration and imaging. For clinical N staging:

1. Nx: not assessed
2. N0: No regional lymph node spread
3. N1: Metastases to ipsilateral level I, II axillary lymph nodes that is movable
4. N2: Metastases to ipsilateral level I, II axillary lymph nodes that is fixed or matted or metastases to internal mammary nodes with no clinically evident axillary lymph node. This is further divided into
    a. N2a: Metastases in ipsilateral level I, II axillary lymph nodes
    b. N2b: Metastases to ipsilateral internal mammary nodes with no axillary lymph node involvement
5. N3: Metastases to ipsilateral level III infraclavicular axillary lymph node, or ipsilateral internal mammary lymph node involvement in addition to level I, II axillary node metastases, or metastases to supraclavicular lymph node. This is further divided into
    a. N3a: Infraclavicular lymph node involvement
    b. N3b: Internal mammary lymph node and axillary lymph node involvement
    c. N3c: Ipsilateral supraclavicular node involvement [16], AJCC Classifications.

For pathological staging:

1. PN0: no regional lymph node metastases histologically
2. PN1: Micrometastases in one to three axillary lymph nodes, and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy
3. PN2: Metastases in four to nine lymph nodes, or in clinically detected internal mammary lymph nodes with no axillary lymph node involvement
4. PN3: Metastases in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or clinically detected ipsilateral internal mammary lymph node with level I, II axillary lymph node involvement, or in greater than three axillary lymph nodes combined with internal mammary lymph involvement that is not clinically detected, or supraclavicular lymph node involvement ipsilaterally [16].

Metastasis classification is defined as follows:

1. M0: No evidence of distant metastases
2. cM0: No evidence clinically or radiographically, but positive findings of microscopically detected tumor cells in blood, bone marrow, or other nonregional nodal tissues.
3. M1: Distant detectable metastases [16].

The AJCC 7th Staging for Breast Cancer uses the TNM staging to give an overall cancer stage (AJCC):

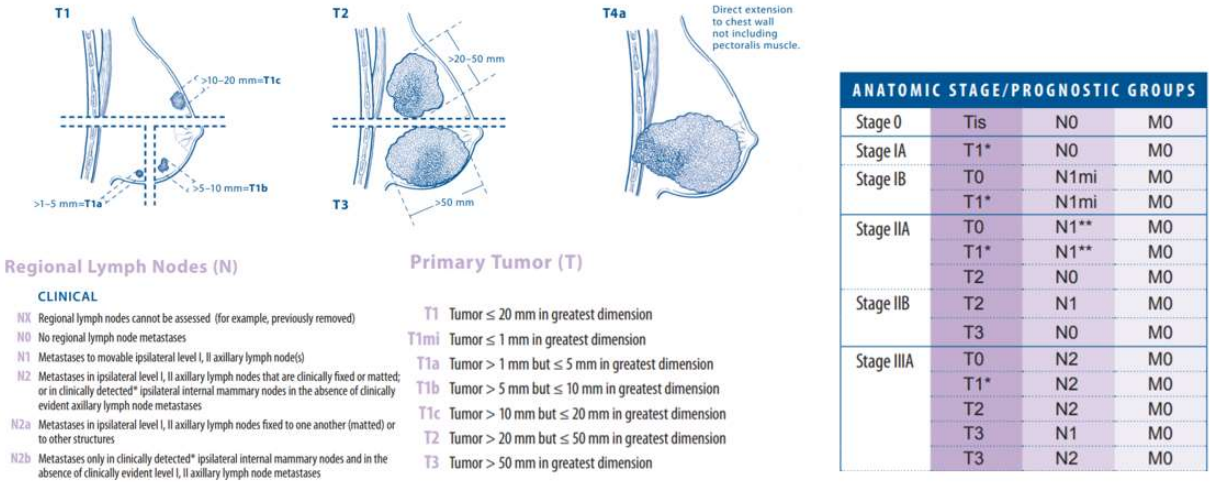
1. Stage 0: Tis, N0, M0
2. Stage IA: T1, N0, M0
3. Stage IB: T0-T1, N1 (micrometastases only), M0
4. Stage IIA: T0N1M0, T1N1M0, T2N0M0
5. Stage IIB: T2N1M0, T3N0M0
6. Stage IIIA: T0N2M0, T1N2M0, T2N2M0, T3N1M0, T3N2M0

7. Stage IIIB: T4N0M0, T4N1M0, T4N2M0

8. Stage IIIC: Any T, N3M0

9. Stage IV: Any T, any N, M1

Figure 1: TNM staging influences the overall AJCC early cancer staging.



ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0

Early stage breast cancer, defined as a malignancy that has not spread beyond the breast or axillary lymph nodes, designated as DCIS, stage I, stage IIA, stage IIB, and stage IIIA breast cancers [17].

Treatment

Breast cancer treatment plans are heavily contingent on the stage at which they are discovered. For early stage breast cancer patients, primary surgery, with or without subsequent radiation therapy depending on type of surgery, is the definitive local treatment. Following this, patients may be offered subsequent adjuvant systemic therapies based on their cancer characteristics. For patients with locally advanced disease, neoadjuvant therapy may be used to induce a tumor response before surgery. Metastatic breast cancer patients usually receive palliative treatment, including systemic therapy, with symptom control and quality of life being the primary focus since at this time metastatic breast cancer is considered not curable but may be controlled for varying lengths of time.

Surgery

Surgery is an extremely important pillar in breast cancer treatment. The first breast surgery in the United States was performed by Williams Halsted in 1882, and consisted of total removal of the breast, the underlying pectoralis major and pectoralis minor, and levels I, II, III lymph nodes of the axilla [18]. Known as the Halsted radical mastectomy, the surgery was extremely disfiguring and stressful for patients but, for the first time, made a definitive difference in disease mortality [19]. In addition, attempts by pioneering surgeons to increase the tissue that was taken, i.e. to make the procedure more radical, did not result in greater survival rates [20]. These results led to a shift towards less disfiguring surgical methods. In 1948, Patey and Dyson began championing the concept of a modified radical mastectomy: removal of the cancerous breast and the levels I, II, III lymph nodes, but sparing the muscles underneath [21]. By the 1970s, this procedure had become widely accepted. However, breast surgical conservation efforts continued. Toth and Lappert introduced the skin-sparing mastectomy in 1984. While still removing the entire breast and allowing access to lymph nodes, the procedure makes a concerted effort to preserve the overlying breast skin [22]. During this time period, Veronesi et al. published the landmark results of the Milan study, concluding that there were no survival differences between a quadratectomy combined with a radiotherapy technique compared to a mastectomy [23]. This conclusion, along with results from the visionary trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP), highlighted the safety of breast conserving surgery (BCS) combined with whole breast irradiation when compared to traditional modified radical mastectomies [24]. Breast conserving surgery must be comprised of a lumpectomy (segmental mastectomy) plus radiation therapy. This allows patients with invasive breast cancer to preserve their breast without sacrificing overall prognosis.

While breast conserving therapy became more mainstream, mastectomies remained a viable treatment option. Surgical advances such as nipple-sparing mastectomy (NSM) were first introduced in

1999. This type of procedure preserved the dermis and epidermis of the nipple while removing the underlying ducts, thus achieving a greater level of breast conservation. Several studies have reported that there are no differences in the recurrence rates between NSM and other forms of mastectomies [25-27]. Surgeons offering this form of treatment must be highly selective with the patient population. Due to the risk of cancer involvement of the nipple, this technique has been limited to use in women with peripheral tumors. However, there is evidence that the procedure may be safe for certain tumors near the nipple areolar complex [28].

Radiation

Radiation therapy is the second broad category of treatment in breast cancer. This type of therapy uses protons, electrons, or photons to deliver pinpoint dosing of radiation to cancer cell DNA, generating lethal double-stranded breaks. The most common type of delivery mechanism for breast cancer treatment is external beam radiation, fueled by either radioactive isotope decay or linear accelerators. Treatment planning is crucial for a successful treatment; proper imaging, delineation of the target fields, dosing and scheduling are necessary to ensure that the maximum tumor volume is targeted with minimal compromise of healthy tissue. Side effects of radiotherapy include toxicity to the skin, muscles, and organs of the irradiated area, fibrosis, and prolonged wound healing. Long term toxicities to the heart and lung are also possible.

Radiation therapy is an important component of care for patients with non-metastatic breast cancer. Whole breast radiotherapy (WBRT) is indicated for patients with early stage breast cancer who underwent breast conserving therapy. The benefits of this procedure are well demonstrated: a twenty-year study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) involving over 1800 patients found no significant differences between patients undergoing BCS and radiation or total mastectomy in terms of disease-free survival, distant-disease-free survival, or overall survival [29]. This

finding is also validated by a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group involving over 10,000 patients across 17 separate trials; the researchers discovered a greater than 40% reduction in 10-year risk for cancer recurrence for BCS patients who underwent radiation therapy compared to BCS alone (19 versus 35 percent, respectively, relative risk [RR] 0.52, 95% CI 0.48-0.56). A reduction in 15-year cancer death was also observed (21% from 25%, CI .75-.9) [30]. Conventional dosing schedule calls for 1.8 to 2 Gy daily fraction to be delivered over 4-5 weeks for a total dosage of 45-50gy. A hypofractionated regimen, with higher dosing but a shorter dosing schedule, can be delivered as an alternative in patients who are older than 50 with early stage (pT1-2N0) estrogen receptor positive disease compliant with endocrine therapy [31]. Radiation may also be given to the tumor bed in selected cases following WBRT to decrease recurrence rates; this is known as a radiation therapy *boost*.

While WBRT is the predominant treatment post BCS, there are a few exceptions to this rule. Older patients with stage I and early node-negative stage II, hormone receptor-positive breast cancer may be excluded from radiation therapy if they are receiving the appropriate endocrine therapies [32]. Rather than receiving WBRT, patients older than 50 years old with small, hormone receptor-positive, lymph node negative tumors may receive accelerated partial breast irradiation (APBI) instead. APBI is a relatively recent development, and results from prospective trials comparing it to WBRT are still pending. According to the American Society of Radiation Oncology (ASTRO) consensus guidelines, patients are suitable for APBI is they are ≥ 60 years of age, BRCA1/2 mutation negative, HER2 negative, ER/PR negative, have unicentric tumor size ≤ 2 cm, negative margins, in T1pN0 stage, and must not have DCIS [33].

Postmastectomy radiation therapy has been shown to decrease cancer recurrence and lead to increased overall survival for certain patient populations. A meta-analysis by Clarke et al. of over 42,000

patients saw a five-year local recurrence risk of 6% in patients receiving postmastectomy radiotherapy versus 23% for those who did not. There was an overall mortality reduction of 4.4% (p=.0009) [34]. The American Society of Clinical Oncology (ASCO) recommends that the following patients receive postmastectomy radiation: patients with 4+ positive axillary lymph nodes, patients with T3 positive axillary nodes, and operable stage III tumors [35]. Patients with positive margins, defined by the presence of ink along the edges of resected tissue removed during mastectomy, should also receive radiation. During treatment, it is imperative that radiation be delivered to both the chest wall and regional nodes (supraclavicular, infraclavicular, and internal mammary nodes). However, for patients who underwent a complete axillary dissection, radiation therapy should be limited to breast/chest wall, as well as the supraclavicular and infraclavicular regions (omitting the axillary field) to avoid lymphedema [36]. Other radiation options for patients include brachytherapy and intraoperative radiation therapy. Radiation is also used for palliative treatments in patients with late stage metastatic disease to decrease primary tumor burden, particularly in large and uncontrolled lesions. Patient may also receive radiotherapy for distant metastatic sites, such as bone, brain, and spinal cord.

Chemotherapy

There is a wide variety of chemotherapy regimens used in patients with breast cancer. In order to select the correct drugs, individual tumor characteristics must be known. Patients with hormone receptor-positive malignancies may benefit more from endocrine therapy rather than traditional chemotherapy therapy. Similarly, patients with HER2-positive cancers will benefit from regimens that target this trait. For patients with estrogen receptor/progesterone receptor and HER2 negative disease, traditional chemotherapy may be administered. Staging at diagnosis is also important. The latest ASCO guidelines for adjuvant treatment in early stage operable tumors recommend the use of chemotherapy based on identified risk factors.

Patients with locally advanced breast cancer are good candidates for neoadjuvant chemotherapy, delivered prior to surgery in order to reduce initial tumor size, thus facilitating the goal of primary surgical resection. Patients with operable tumors may also receive neoadjuvant chemotherapy to achieve better postoperative cosmetic outcomes by minimizing the tissue needed to be resected. While this strategy is associated with a higher likelihood of surgical success and clinical response, it does not improve disease-free survival or overall survival compared to adjuvant chemotherapy [37]. Patients with hormone receptors-positive disease may be given chemotherapy along with endocrine therapy during their neoadjuvant treatments, while HER-2 positive patients should be given HER-2 targeting agents such as Trastuzumab. Following surgery, patients who received the full neoadjuvant regimen will have different adjuvant treatments. Hormone receptor positive breast cancer patients should continue further endocrine therapy without further chemotherapy. Patients with hormone receptor positivity should receive HER-2 agents without further chemotherapy [38, 39].

The purposes of chemotherapy treatment for metastatic breast cancer are to prolong survival and maximize quality of life. Because every patient's cancer is unique, there is no broad treatment regimen that can be used for all situations. Factors that must be considered include tumor burden, patient's health status, patient dosing and scheduling conflicts, etc. Single agent therapies and combination chemotherapy regimens, with or without endocrine and HER-2-targeted therapies, are all acceptable treatment plans. Chemotherapy should be continued until progression of disease or as tolerated because it modestly improves overall survival and substantially improves progression-free survival, but this should be balanced against toxicity and decreases in quality of life. Palliative care should be offered throughout the care process. It is extremely important that the clinicians understand the diminishing return of chemotherapy in patients with advanced disease and knows when to pursue

other avenues of care instead. Short breaks, flexibility in scheduling, or a switch to endocrine therapy (in patients with hormone receptor–positive disease) may be offered to selected patients.

Targeted Immunotherapies

Breast cancer is a heterogeneous disease with complex genomic subtypes. One of its most well-researched oncogene is the human epidermal growth factor receptor-2 (HER-2), which is present in up to 20% of primary invasive breast cancers [40]. All clinicians must request HER-2 testing on every primary invasive breast cancer. For patients with positive tests, HER-2-directed therapy is a critical component of their adjuvant therapy. Trastuzumab (Herceptin) is a monoclonal antibody that inhibits HER-2's growth signals to cancer cell. Herceptin plus chemotherapy is recommended for all patients with HER-2 positive, node-positive breast cancer and HER-2 positive, node-negative cancer > 1 cm. Cardiac toxicity is a well-known side effect of Trastuzumab treatment, and patients should undergo routine cardiac monitoring throughout the duration of therapy. Another HER-2 monoclonal antibody is Pertuzumab, which can be incorporated into adjuvant treatment along with Trastuzumab and chemotherapy. However, its overall benefit is currently unknown; a phase III trial of the drug (APHINITY trial) is currently underway.

Why is Guideline Concordant Care Important?

Breast cancer is a complex, multifocal disease with a wide variety of treatment regimens. The need to address all these variables adequately makes the task of mapping out a treatment regimen challenging for even the most seasoned of clinicians. Decades of clinical research and billions of research dollars have led to series of multidisciplinary guidelines that aim to improve quality of care and reduce unnecessary treatments. However, not all guidelines are created equal. Evidence-based guidelines involve a systematic process that critically assesses the whole body of scientific literature surrounding a particular topic. The most rigorous of these sources involves well-designed cohort studies, randomized clinical trials, and large-scale meta-analyses. However, grey areas of knowledge still surround the islands

of proven scientific conclusions due to new technologies, discrepancies between experts, or on-going research. To address these concerns, many professional organizations have implemented consensus-based guidelines. These represent an agreement among a panel of experts for what the ideal approach to diagnosis or treatment should be for a topic that is not heavily supported by available scientific data.

For breast cancer, the most utilized treatment guidelines include the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO). It is interesting that while there were many points of concordance between the two organizations, there are also several points of discrepancy, especially when newer, less-evidence-based issues are addressed. It is important to note that these are merely guidelines meant to help the physician with clinical decision-making, and are not legally binding. The sheer complexity of breast cancer defies any attempt to force its therapeutic strategy into a straightforward algorithm. While the ESMO grades its guidelines for both level of evidence and grade of recommendations, the NCCN only uses grades of recommendation [41]. Divided from category 1 (high-level evidence) to Category 3 (based on upon any level of evidence), NCCN guidelines are all consensus-based. Because of this, it is not surprising that discrepancies arise between well-established guidelines when addressing topics that have not be completely researched by research or clinical trials.

ASCO clinical practice guidelines were historically dependent on a high-quality body of evidence that could form strong evidence-based decisions. Although ASCO does not address topics in breast cancer as comprehensively as does the ESMO or the NCCN, all the clinical practice guidelines are evidence-based and a result of a systematic literature review. The organization has traditionally avoided certain clinical questions with limited evidence. However, in 2010, the ASCO board of directors approved the development of a formal consensus methodology, where consensus recommendation can be applied to guidelines or just selected clinical questions [42]. Of note, the consensus process still

required a rigorous review of the literature. This was done to meet the needs of ASCO's membership and illustrates an important point: often, topic areas with discrepancies but lacking the most evidence, are the subjects that require the most guidance. Thus, the consensus approach will always be needed to form a comprehensive series of practice guidance.

There is extensive evidence suggesting that adhering to guideline-concordant therapies has a beneficial effect on patient outcome. Adhering to guideline-directed treatment has been shown to reduce healthcare costs, reduce hospital length of stay, and reduce detrimental variations in treatment [43]. A direct effect on patient outcome has also been shown as well. Grimshaw & Russell identified 59 evaluations of scientifically rigorous clinical guidelines and found that 55 of them resulted in significant improvement of care after their subsequent introduction [44]. The benefits are quite clear in breast cancer specifically. A study of over 1500 breast cancer patients found that the hazard ratio for patients not treated with guideline concordant therapy was 2.3 (95% 1.3-4.0) in patients with moderate recurrence risk and 2.7 (95% 1.9-3.9) in patients with high recurrence risk [45]. Another study performed in Rhode Island tracked over 490 breast cancer patients over five years and noted that patients who did not receive definitive therapy had a higher risk of recurrence (hazard ratio 1.7; 95% CI: 1.0-2.5) and breast cancer-specific mortality (hazard ratio 2.2; 95% CI: 1.2-3.9) during the first five years of follow-up [46]. Wu et al. analyzed over 2,362 breast cancer patients and found that racial differences in guideline-concordant care led to a 2.35 times higher chance of all-cause mortality after controlling for age. Importantly, this difference in all-cause mortality was reduced after controlling for appropriate treatment and clinical variables [47].

Barriers to Guideline Concordant Care

Evidence of ethnic/racial disparities in breast cancer treatment are difficult to conclude due to conflicting reports and varying study designs. Most of the studies have focused on African Americans,

and there is relatively little literature about other racial groups. While breast cancer mortality for Caucasian women has decreased an average rate of 2.4% annually since 1990, black women have only seen their mortality decrease by 1.1% per year during the same time period. Despite lower incidence rates, black patients suffer a higher breast cancer mortality rate compared to white patients [48]. There are numerous factors that account for this discrepancy. Black women have higher rates of irregular mammography screenings and delays in follow-up post-screening [49, 50]. They also have differences in co-morbidity factors, including higher base rates of hypertension, cardiovascular disease, and diabetes that may adversely affect treatment regimens [51]. Black patients also have higher incidences of worse prognosis disease, such as triple negative breast cancer [52]. Van Ravesteyn et al.'s study of mortality differences between white and black breast cancer patients found that the higher mortality in African Americans can be attributed to co-morbid diseases, differences in adjuvant therapy use, disparate mammography screening, and other unexplained factors [53].

Freedman et al.'s study suggested that, compared to Caucasians, black and Hispanic women were more likely to be younger at diagnosis, uninsured or insured by Medicaid, and have advanced disease. They also found that the two ethnic populations had lower rates of chemotherapy treatment, even after stratifying for insurance status and socioeconomic income [54]. Hassett et al.'s retrospective review of California and New York on guideline concordant therapy in patients based on race/ethnicity found that African Americans had lower odds of receiving recommended breast surgery, and hormone therapy compared to Caucasians. However, they did have a higher chance of receiving the proper chemotherapy. The researchers also looked at other races/ethnicities: while Hispanics in California had similar disparities, Hispanics in New York had the same odds of guidelines concordant care as white patients. While Asian-Pacific Islanders in New York had the same percentage of guideline-concordant

therapy compared to white patients, Asian-Pacific Islanders in California had a greater chance of receiving the recommended chemotherapy, radiation, surgery, and hormone therapy [55].

While Hassett et al. only looked at two states, Anderson et al.'s review encompassed 7 states and over 6000 nonmetastatic breast cancer patients. They found a nonconcordance rate of 12%, with the most common omissions being radiotherapy post BCS and lymph node dissection. Treatment failure was linked with facilities that lacked comprehensive services and integrated referral systems. However, this link may be confounded by the fact that these facilities, usually Non-Commission on Cancer – accredited hospitals, are in rural, poverty-stricken, lower educational areas. Older women with BCS were more likely to miss radiotherapy, as well as patients in more affluent areas [56].

Wu et al. found that adherence to guideline-concordant chemotherapy was significantly lower in Medicare/Medicaid beneficiaries, high-poverty, lower-education, and non-Commission on Cancer-accredited hospitals. Even after adjusting for age and clinical variables, living in high-poverty areas was associated with decreased chemotherapy and hormonal treatment [57]. These results were confirmed by Guy et al., whose analysis of a rural region in the United States showed that higher socioeconomic status was associated with guideline-concordant adjuvant therapy and chemotherapy. Interestingly, they noted that Medicaid was associated with guideline-concordant chemotherapy compared to private insurance [58]. Higher education was also found to a predictor for hormonal therapy concordance [59].

Treatment concordance appears to be affected by insurance status. Hassett et al.'s study of guideline concordance in New York and California residents showed that Medicaid-insured patients were less likely to receive the proper breast surgery, lymph node surgery, radiation therapy, and hormone therapy [55]. Freedman et al.'s study also showed that lack of insurance, Medicaid, Medicare, and unknown insurance were associated with decreased odds of receiving the proper chemotherapy regimen compared to private insurance [54]. Having Medicaid also increased the likelihood that a

patient post BCS did not receive the proper radiation therapy or experience interruptions during therapy [60].

Patient beliefs and preferences can also present a challenge to guideline concordance. Specifically, a survey of 258 women found that lack of patient knowledge and medical mistrust are associated with underuse of proven adjuvant therapies [61]. Up to one third of adjuvant treatment underuse is due to patient refusal [62]. While this decision may be informed and justified when accounting for other factors such as age and comorbidities, it may also be due to a lack of knowledge about the consequences and benefits of these treatments. It is also concerning that physician efforts to educate patients on treatment options are highly dependent on the patient's trust in the clinician, rather than the amount of information or the way it is presented [63]. This disconnect presents a challenge to ensuring adequate patient knowledge when making informed treatment choices.

Databases

There are several nationwide databases that are used for epidemiological studies. Specifically, the National Cancer Data Base (NCDB) is a clinical oncology database (not population-based) jointly compiled by the American College of Surgeons and the American Cancer Society that includes hospital registry data on more than 1,500 Commission on Cancer-accredited facilities. These data represent around 75-85% percent of all newly diagnosed cancer cases nationwide, making the database more representative and generalizable to the US population compared to some other national databases. The NCDB dataset codes for facility-level data, such as type of practice, in addition to patient demographics and clinical/tumor variables. It also includes detailed information about socioeconomic factors such as insurance status. Area-based education and income were derived at the zip code level.

Thesis Proposal

Due to the advantages of the NCDB, we proposed to use the database for the following purposes:

- **Aim 1**- To determine the association between socioeconomic, clinical, patient, and facility factors and the receipt of evidence-based treatment (immunotherapy, chemotherapy, and post-breast conserving surgery radiation (PBCS RT)) for women with early-stage breast cancer for whom treatment is recommended by clinical guidelines
    - Hypothesis- Facility type, race, insurance type, education, and urbanicity is associated with receipt of evidence-based treatment recommendations
- **Aim 2**- To validate previous findings in a large, national sample relating receipt of evidence-based treatment and improvements with overall survival.
    - Hypothesis- Receipt of evidence-based treatment improves overall survival in patients for whom treatment is recommended

Methods

Data Source and Study Population

NCDB data have been characterized elsewhere [64], and data were coded and reported using standard protocols. Emory University was granted access to the NCDB breast cancer Participant User File (PUF), which contains 2246280 patients diagnosed between January 1st, 2004 and December 31st, 2014. The study was limited to women 18 years or older with a diagnosis of American Joint Committee on Cancer (AJCC) stages I to IIIA breast cancer who received all or part of their first course of therapy in the reporting facility. The study excluded patients with prior cancer diagnoses, missing survival data, and who received palliative care treatment only. When examining chemotherapy and immunotherapy concordance, patients with missing data for hormone receptor or HER-2 status were also excluded.

Study Variables

The following treatment protocols were examined:

1) Post-operative radiation for breast conserving surgery

2) Chemotherapy

3) Immunotherapy

*Receipt of surgery was initially examined, but our analysis found that compliance for this treatment was essentially 100%.

The population was divided into 2 groups, those who received evidence-based therapy versus patient who did not. Variables examined included facility level data such as facility type, geographic location, and hospital distance from patient. Facility type included community cancer programs, comprehensive community cancer programs, academic/research programs, and integrated network cancer programs. Patient demographic data included age at diagnosis, race, and insurance status, all of which were analyzed as categorical variables. Charlson Comorbidity Index was used to represent patients comorbidity status [65]. Cancer characteristics were measured using pathologic T/N staging and ER and PR status. These were analyzed as categorical variables. Socioeconomic status was measured using area-based indicators of income derived from the 2000 US Census data and educational level derived at the zip code level from both the 2000 US Census data and the 2012 American Community Survey data.

Statistical Analysis

Descriptive statistics were reported for each variable; univariate association (UVA) of each covariate with the receipt of immunotherapy was assessed using chi-square test for categorical variables. We then investigated the socioeconomic, clinical, and facility factors associated with receipt of

immunotherapy using logistic regression modeling. The propensity score matching (PSM) method was conducted to address potential selection bias. Odds ratios (ORs) and 95% confidence intervals were calculated in the regression models. A $p < 0.001$ was considered statistically significant given the large sample size.

Overall survival was measured in months from date of diagnosis to date of either death or last follow-up. A multivariable Cox proportional hazard model (MVA) model was fit using backward variable selection method to select the covariates; an alpha value of .2 was set as the removal criteria. An extended Kaplan-Meier estimator was plotted to compare patients, with log-rank P value of $< .05$ considered to be statistically significant. Statistical analysis was conducted using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC) and SAS macros developed by the Biostatistics and Bioinformatics Shared Resources at Winship Cancer Institute at Emory University in Atlanta, Georgia.

Post-Breast Conserving Surgery Radiation

Clinical trials have confirmed it is imperative that RT be administered after BCS. Clarke et al. found that five year local recurrence risk dropped from 26% to 7% with radiation, while 15 year mortality dropped from 35.9% to 30.5% [34]. A meta-analysis reported that the 10-year risk of any first recurrence was 19.3% in women allocated to BCS plus RT versus 35% in women allocated to BCS only; post-BCS RT also reduces overall breast cancer death rates by one-sixth [66]. The importance of receiving RT after breast conserving surgery in this scenario is highlighted by the numerous national evidence-based guidelines that recommend it [67-69]. In addition, post-BCS RT is a Rapid Quality Reporting System (RQRS) quality metric for all Commission on Cancer (CoC)-accredited cancer programs, reinforcing its status as a quality improvement tool which seeks to provides real clinical time assessment of hospital level adherence to quality of cancer care measures.

Post BCS RT from 2004 to 2013

There were 612,878 early-stage breast cancer patients who received BCS between 2004 to 2013. **Figure 2** illustrates the patient selection and exclusion criteria. The median age of the entire cohort was 62 years old. The median follow-up was 61.04 months. A total of 599,646 patients received RT within 1 year of surgery; 13,232 patients did not. Overall compliance to treatment was 97.8%. Baseline characteristics and unadjusted outcomes between eligible patients who received post-BCS RT and who did not receive post-BCS RT are reported in **Table 1**.

Factors Associated with BCS RT Treatment

On UVA (**Table 2**), factors found to be associated with use of PMRT included treatment at an integrated network cancer program (98.5% compliance). Geographically, the Midwest (98.7%) and South (98.6%) had the highest rates of compliance, with the West (95.1%) having the lowest rate. Patient characteristics associated with increased treatment includes being older than 75, having a Charlson Deyo score of 2 (versus 0 and 1), being black, having no insurance, earning between $30,000 and $35,999, living in an area with 80.1%-86% high school graduation rate and living less than 5 miles away from treatment center. Tumor characteristics associated with increased compliance are unknown N staging and T3 staging.

On MVA (**Table 3**), being treated at an integrated network cancer program, treatment facility location in the Midwest, Northeast, South (versus West), diagnosis age < 75 years old (versus > 75 years old), making less than $46,000, living in an zip code with greater than 83% adult high school graduation rate, living in an urban setting (versus metro), treatment facility located < 15 miles from the patient's home zip code, having a Charlson Deyo score (index of morbidity) of 2 (versus 0 or 1), having unknown N staging, and being diagnosed earlier than 2013 were associated with increased compliance.

Impact of BCS RT on OS

The median follow-up was 61.04 months. The five-year OS rate was 44.7% for patients treated with PBCS RT versus 40.8% for patients not treated with PMRT (P<.001) (Figure 2). Use of PBCS RT was found to be associated with improved OS on UVA (Unadjusted HR: 0.71 (95% CI 0.66-0.77) P<.001) (**Table 4**) and MVA (Adjusted HR: .81 (95% CI.76-.868)). On MVA (**Table 5**), additional factors found to be associated with improved OS included being treated at an integrated network cancer program, facility location located in the Northeast and South regions, age $\leq$ 65, having private insurance, making more than $46,000, living in a zip code with greater than 83% adult high school graduation rate, having a Charlson Deyo score of 0, and having earlier tumor staging (N0). Interaction tests revealed that influence of PBCS RT on OS was not dependent on the different levels of other variables associated with OS on MVA, indicating a benefit of PBCS RT across all strata within these variables. Kaplan Meier curve (**Table 6**) shows significant differences in overall survival between compliance with treatment and noncompliance.

Discussion

We investigated relevant factors associated with receipt of guideline concordant radiation in patients who underwent breast conserving surgery. From 2004 to 2013, we found that the percentage of patients concordant who received guideline-concordant care remained relatively constant. Receipt of radiation therapy after breast-conserving surgery for eligible patients has been high in other studies as well, with over 95% compliance [70]. The benefits of post breast conserving surgery radiation is well documented [66], and it has been the standard of care for the past 15 years so these rates of concordance are encouraging. We also demonstrated the importance of concordance as we found that the absence of radiation treatment post-BCS was associated with a 19% relative risk increase in mortality. This is in line with the relative risk reduction of one-sixth seen in the literature [66].

Facility type was associated with guideline concordant radiation. Integrated Network Cancer programs, a designation given by the Commission on Cancer (COC) for large, often academic, multi-center programs, were significantly more likely to treat post-BCS patients with radiation. Integrated Network Cancer programs must be in good standing with a unified cancer committee, coordinated service locations, and multidisciplinary physicians. This finding correlates with previous studies where facility type has also been found to influence receipt of guideline concordance adjuvant systemic therapy [57].

Facility location was also a factor in determining guideline concordant radiation treatment. Patients in the West and were the most likely to underuse radiation therapy post BCS. Similar disparities have been found in patients who require adjuvant endocrine therapy [71]. Other geographic differences have also been documented [72, 73], and could significantly affect breast cancer mortality in these patients.

Age also played a role in radiation treatment. Patients who were younger were significantly more likely to receive radiation treatment. Several studies have examined the viability of omitting RT for older patients. A Cancer and Leukemia Group B (CALGB) clinical trial examined women aged greater than 70 years with ER positive breast cancer who underwent BCS, and concluded that radiation therapy lowered risk of local recurrence but did not significantly lower risk of subsequent mastectomy or death [74]. However, Albert et al. examined the SEER clinical database and concluded that guideline concordant radiation therapy after BCS was associated with greater breast preservation for most older women outside of a clinical trial [75]. Omitting such treatments in relatively healthy patients simply due to age could negatively affect the outcome for these patients.

Education disparities was also a barrier to breast cancer treatment compliance in our study, which is in concordance with other regional studies [76, 77]. Other studies have shown that women living in

areas of greater education were more likely to receive treatment BCS plus radiation treatment compared to BCS only. Comorbidity was found as a predictor for compliance; specifically, future research should consider how these comorbidities should be accounted for when determining the need for radiation.

To our knowledge, this study has one of the largest number of patients used to examine the predictors of post BCS radiation. We found that post BCS radiation significantly improved OS in women with early stage breast cancer after accounting for multiple factors impacting OS through statistical testing including UVA, MVA, and interaction tests. Radiation treatment post-BCS was associated with a 19% relative risk decrease in mortality. This is in line with the relative risk reduction of one-sixth seen in the literature (EBCTC, 2011).

The study had several strengths and limitations. The strengths of the study include a large number of early stage breast cancer patients derived from a national dataset representing a large number of diverse institutions. We also performed other methods to reduce bias, included stratified analysis and interaction effect testing. What about propensity score matching? However, we did not examine the possible reasons for radiation omission for those patients who did not receive RT, which could have been justified for clinical reasons. It must also be noted that despite clear guidelines regarding post BCS radiation, the ultimate clinical judgment rests with the treating physician, and there may be valid reasons for why the patient did not receive treatment. Retrospective databases in general do not illuminate the reasons why certain care was or was not delivered. Also, with the very large number of cases included, many variables may be significantly different due to the extreme volume involved.

Post Breast Conserving Surgery Figures:

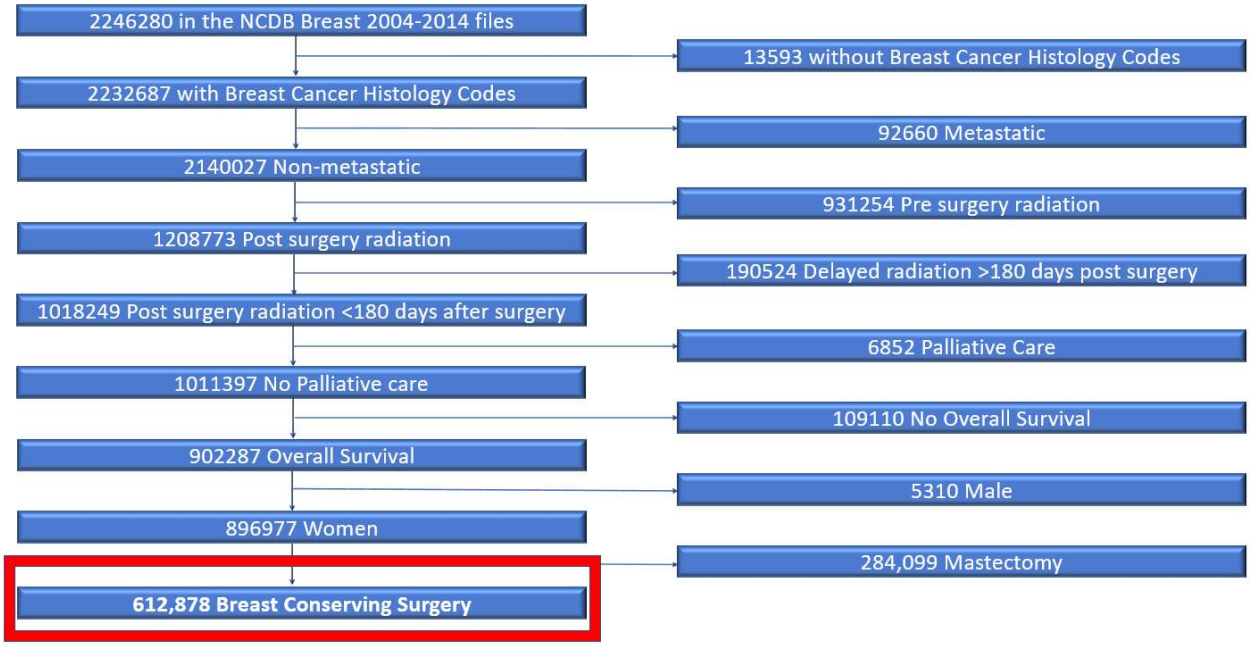


Figure 2: Selection Criteria for Post-Breast Conserving Surgery Radiation Therapy Study

Table 1: Descriptive Statistics for All Variable: Post-Breast Conserving Surgery Radiation

Variable	Level	N (% within category) = 612878
Receipt of Post BCS Radiation	No	13232 (2.2)
	Yes	599646 (97.8)
Facility Type	Community Cancer Program/Other	67274 (11.0)
	Comprehensive Community Cancer Program	301332 (49.2)
	Academic/Research Program	180518 (29.5)
	Integrated Network Cancer Program	63754 (10.4)
Facility Location	Northeast	152683 (24.9)
	South	194541 (31.7)
	Midwest	160156 (26.1)
	West	105498 (17.2)
Age at Diagnosis (C)	<65	263533 (43.0)
	65-75	246299 (40.2)
	>75	103046 (16.8)
Race	White	527370 (86.0)
	Black	62982 (10.3)
	Other	22526 (3.7)
Insurance Type	Not Insured	8855 (1.4)
	Private Insurance	322879 (52.7)
	Government Insurance	281144 (45.9)

Variable	Level	N (% within category) = 612878
Median Income Quartiles 2000	< $30,000	58988 (9.6)
	$30,000 - $35,999	90924 (14.8)
	$36,000 - $45,999	162823 (26.6)
	$46,000 +	300143 (49.0)
Percent No High School Degree Quartiles 2000	>= 29%	76412 (12.5)
	20 – 28.9%	123395 (20.1)
	14 – 19.9%	143831 (23.5)
	< 14%	269240 (43.9)
Urban/Rural 2003	Metro	530425 (86.5)
	Urban	73652 (12.0)
	Rural	8801 (1.4)
Distance	<= 5 miles	204454 (33.4)
	5 - 10 miles	156113 (25.5)
	10 - 15 miles	85188 (13.9)
	> 15 miles	167123 (27.3)
Charlson-Deyo Score	0	523361 (85.4)
	1	74572 (12.2)
	2	14945 (2.4)
Pathologic T	T1	516779 (84.3)
	T2	92654 (15.1)
	T3	3445 (0.6)

Variable	Level	N (% within category) = 612878
Pathologic N	N0	443512 (72.4)
	N1	70053 (11.4)
	N2	11361 (1.9)
	NX	87952 (14.4)
Year of Diagnosis	2004	29048 (4.7)
	2005	31778 (5.2)
	2006	35015 (5.7)
	2007	41835 (6.8)
	2008	64072 (10.5)
	2009	74884 (12.2)
	2010	77129 (12.6)
	2011	83658 (13.7)
	2012	85440 (13.9)
	2013	90019 (14.7)

***Percentage is calculated within each individual category**

Table 2: Univariate Association with Study Cohort: Post Breast Conserving Surgery Radiation

		Receipt of Radiation		
Covariate	**Level**	**No (%) =13232**	**Yes (%)=599646**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	1399 (10.6)	65875 (11.0)	**<.001**
	Comprehensive Community Cancer Program	6236 (47.1)	295096 (49.2)	
	Academic/Research Program	4652 (35.2)	175866 (29.3)	
	Integrated Network Cancer Program	945 (7.1)	62809 (10.5)	
Facility Location	Northeast	3604 (27.2)	149079 (24.9)	**<.001**
	South	2560 (19.4)	191981 (32.0)	
	Midwest	1931 (14.6)	158225 (26.4)	
	West	5137 (38.8)	100361 (16.7)	
Age at Diagnosis (C)	<65	5870 (44.4)	257663 (43.0)	**<.001**
	65-75	5636 (42.6)	240663 (40.1)	
	>75	1726 (13.0)	101320 (16.9)	

		Receipt of Radiation		
Covariate	**Level**	**No (%) =13232**	**Yes (%)=599646**	**Parametric P-value***
Race	White	11369 (85.9)	516001 (86.0)	**<.001**
	Black	1103 (8.3)	61879 (10.3)	
	Other	760 (5.7)	21766 (3.6)	
Insurance Type	Not Insured	137 (1.0)	8718 (1.45)	**<.001**
	Private Insurance	7351 (55.6)	315528 (52.6)	
	Government Insurance	5744 (43.4)	275400 (45.9)	
Median Income Quartiles 2000	< $30,000	1105 (8.4)	57883 (9.7)	**<.001**
	$30,000 - $35,999	1622 (12.3)	89302 (14.9)	
	$36,000 - $45,999	3393 (25.6)	159430 (26.6)	
	$46,000 +	7112 (53.8)	293031 (48.9)	
Percent No High School Degree Quartiles 2000	>= 29%	1919 (14.5)	74493 (12.4)	**<.001**
	20 – 28.9%	2541 (19.2)	120854 (20.2)	
	14 – 19.9%	2931 (22.2)	140900 (23.5)	
	< 14%	5841 (44.1)	263399 (43.9)	

Covariate	Level	Receipt of Radiation: No (%) =13232	Receipt of Radiation: Yes (%)=599646	Parametric P-value*
Urban/Rural 2003	Metro	11686 (88.3)	518739 (86.5)	**<.001**
	Urban	1394 (10.5)	72258 (12.0)	
	Rural	152 (1.2)	8649 (1.4)	
Distance	<= 5 miles	3955 (29.9)	200499 (33.4)	**<.001**
	5 - 10 miles	3030 (22.9)	153083 (25.5)	
	10 - 15 miles	1641 (12.4)	83547 (13.9)	
	> 15 miles	4606 (34.8)	162517 (27.1)	
Charlson-Deyo Score	0	11643 (88.0)	511718 (85.4)	**<.001**
	1	1339 (10.1)	73233 (12.2)	
	2	250 (1.9)	14695 (2.5)	
Pathologic T	T1	10990 (83.0)	505789 (84.4)	**<.001**
	T2	2157 (16.3)	90497 (15.1)	
	T3	85 (0.6)	3360 (0.6)	

		Receipt of Radiation		
Covariate	**Level**	**No (%) =13232**	**Yes (%)=599646**	**Parametric P-value***
Pathologic N	N0	10187 (77.0)	433325 (72.3)	**<.001**
	N1	1676 (12.7)	68377 (11.4)	
	N2	281 (2.1)	11080 (1.9)	
	NX	1088 (8.2)	86864 (14.5)	
Year of Diagnosis	2004	576 (4.4)	28472 (4.8)	**<.001**
	2005	620 (4.7)	31158 (5.2)	
	2006	763 (5.8)	34252 (5.71)	
	2007	934 (7.0)	40901 (6.8)	
	2008	1146 (8.7)	62926 (10.5)	
	2009	1526 (11.5)	73358 (12.2)	
	2010	1606 (12.1)	75523 (12.6)	
	2011	1949 (14.7)	81709 (13.6)	
	2012	2024 (15.3)	83416 (13.9)	
	2013	2088 (15.8)	87931 (14.7)	

Covariate	Level	Receipt of Radiation		
		No (%) =13232	Yes (%)=599646	Parametric P-value*

* The parametric p-value is calculated by chi-square test. Percentage is calculated within each individual category.

Table 3: Multivariable Logistic Regression Model for Post Breast Conserving Surgery Compliance

		Receipt of Post BCS Radiation		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Facility Type	Community Cancer Program/Other	0.64 (0.57-0.71)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	0.77 (0.70-0.83)	**<.001**	
	Academic/Research Program	0.64 (0.58-0.70)	**<.001**	
	Integrated Network Cancer Program	-	-	
Facility Location	Northeast	2.38 (2.25-2.52)	**<.001**	**<.001**
	South	3.89 (3.65-4.14)	**<.001**	
	Midwest	3.79 (3.55-4.05)	**<.001**	
	West	-	-	
Age at Diagnosis (C)	<65	1.28 (1.18-1.38)	**<.001**	**<.001**
	65-75	1.16 (1.08-1.24)	**<.001**	
	>75	-	-	
Insurance Type	Not Insured	1.21 (0.98-1.51)	0.076	**0.019**
	Private Insurance	1.07 (1.01-1.13)	**0.014**	
	Government Insurance	-	-	

		Receipt of Post BCS Radiation		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Median Income Quartiles 2000	< 30,000	1.56 (1.41-1.74)	**<.001**	**<.001**
	30,000 – 35,999	1.50 (1.38-1.63)	**<.001**	
	36,000 – 45,999	1.23 (1.15-1.30)	**<.001**	
	> 46,000	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	0.56 (0.51-0.61)	**<.001**	**<.001**
	20%-29.0%	0.79 (0.74-0.85)	**<.001**	
	14%–19.9%	0.91 (0.85-0.97)	**0.002**	
	< 14%	-	-	
Urban/Rural 2003	Metro	0.75 (0.60-0.93)	**0.008**	**<.001**
	Urban	1.07 (0.86-1.34)	0.522	
	Rural	-	-	
Charlson-Deyo Score	0	0.86 (0.73-1.02)	0.083	**<.001**
	1	1.03 (0.86-1.23)	0.722	
	2	-	-	
Pathologic N	N0	0.70 (0.64-0.76)	**<.001**	**<.001**
	N1	0.63 (0.56-0.70)	**<.001**	
	N2	0.50 (0.40-0.62)	**<.001**	
	NX	-	-	

		Receipt of Post BCS Radiation		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Year of Diagnosis	2004	1.74 (1.57-1.92)	**<.001**	**<.001**
	2005	1.77 (1.60-1.96)	**<.001**	
	2006	1.68 (1.53-1.85)	**<.001**	
	2007	1.62 (1.47-1.78)	**<.001**	
	2008	1.80 (1.63-1.98)	**<.001**	
	2009	1.41 (1.29-1.54)	**<.001**	
	2010	1.43 (1.31-1.56)	**<.001**	
	2011	1.20 (1.11-1.30)	**<.001**	
	2012	1.04 (0.96-1.12)	0.351	
	2013	-	-	
Distance	<= 3.9 miles	1.47 (1.37-1.56)	**<.001**	**<.001**
	3.9 - 8 miles	1.49 (1.39-1.59)	**<.001**	
	8.01 - 16.2 miles	1.47 (1.38-1.57)	**<.001**	
	> 16.2 miles	-	-	

* Number of observations in the original data set = 612878. Number of observations used = 612878.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: race_cat.

Table 4: Univariate Association with Overall Survival: Post Breast Conserving Surgery Radiation

			Last Contact or Death, Months from Diagnosis		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Post BCS Radiation Receipt	Yes	612878	0.71 (0.66-0.77)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	67274	0.89 (0.88-0.90)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	301332	0.88 (0.87-0.88)	**<.001**	
	Academic/Research Program	180518	0.96 (0.96-0.97)	**<.001**	
	Integrated Network Cancer Program	63754	-	**-**	
Facility Location	Northeast	152683	1.06 (1.05-1.06)	**<.001**	**<.001**
	South	194541	1.12 (1.11-1.13)	**<.001**	
	Midwest	160156	1.02 (1.02-1.03)	**<.001**	
	West	105498	-	**-**	
Age at Diagnosis (C)	<65	263533	0.96 (0.95-0.96)	**<.001**	**<.001**
	65-75	246299	1.08 (1.07-1.09)	**<.001**	
	>75	103046	-	**-**	

			Last Contact or Death, Months from Diagnosis		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Race	White	527370	0.87 (0.86-0.88)	**<.001**	**<.001**
	Black	62982	0.95 (0.94-0.97)	**<.001**	
	Other	22526	-	**-**	
Insurance Type	Not Insured	8855	1.08 (1.05-1.10)	**<.001**	**<.001**
	Private Insurance	322879	0.91 (0.90-0.91)	**<.001**	
	Government Insurance	281144	-	**-**	
Median Income Quartiles 2000	< $30,000	58988	1.01 (1.00-1.02)	**0.012**	**0.001**
	$30,000 - $35,999	90924	1.01 (1.01-1.02)	**<.001**	
	$36,000 - $45,999	162823	1.00 (1.00-1.01)	0.221	
	$46,000 +	300143	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	76412	1.05 (1.04-1.06)	**<.001**	**<.001**
	20 – 28.9%	123395	1.01 (1.01-1.02)	**<.001**	
	14 – 19.9%	143831	0.99 (0.99-1.00)	0.121	
	< 14%	269240	-	**-**	

			Last Contact or Death, Months from Diagnosis		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	530425	0.98 (0.96-1.00)	0.050	**0.038**
	Urban	73652	0.99 (0.96-1.01)	0.208	
	Rural	8801	-	-	
Distance	<= 5 miles	204454	0.92 (0.91-0.93)	**<.001**	**<.001**
	5 - 10 miles	156113	0.95 (0.95-0.96)	**<.001**	
	10 - 15 miles	85188	0.97 (0.96-0.98)	**<.001**	
	> 15 miles	167123	-	-	
Charlson-Deyo Score	0	523361	0.82 (0.81-0.84)	**<.001**	**<.001**
	1	74572	0.94 (0.92-0.95)	**<.001**	
	2	14945	-	-	
Pathologic T	T1	516779	1.10 (1.06-1.14)	**<.001**	**<.001**
	T2	92654	1.09 (1.05-1.13)	**<.001**	
	T3	3445	-	-	

			Last Contact or Death, Months from Diagnosis		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	443512	1.08 (1.08-1.09)	**<.001**	**<.001**
	N1	70053	1.05 (1.04-1.06)	**<.001**	
	N2	11361	0.95 (0.93-0.97)	**<.001**	
	NX	87952	-	**-**	

Table 5: Multivariable Cox Proportional Hazard Model for Overall Survival- Post Breast Conserving Surgery Radiation

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Post BCS Radiation Receipt	Yes	612878	0.812 (0.76-0.87)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	67274	1.04 (1.03-1.05)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	301332	1.01 (1.00-1.02)	0.151	
	Academic/Research Program	180518	1.06 (1.05-1.07)	**<.001**	
	Integrated Network Cancer Program	63754	-	-	
Facility Location	Northeast	152683	1.05 (1.04-1.06)	**<.001**	**<.001**
	South	194541	1.01 (1.00-1.02)	**0.009**	
	Midwest	160156	0.98 (0.97-0.99)	**<.001**	
	West	105498	-	-	
Age at Diagnosis (C)	<65	263533	0.99 (0.98-1.00)	0.065	**<.001**
	65-75	246299	0.97 (0.96-0.98)	**<.001**	
	>75	103046	-	-	
Race	White	527370	0.97 (0.96-0.98)	**<.001**	**<.001**
	Black	62982	0.96 (0.95-0.98)	**<.001**	
	Other	22526	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Insurance Type	Not Insured	8855	1.10 (1.07-1.12)	**<.001**	**<.001**
	Private Insurance	322879	0.99 (0.99-1.00)	0.109	
	Government Insurance	281144	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	76412	1.02 (1.01-1.03)	**<.001**	**0.002**
	20 – 28.9%	123395	1.01 (1.00-1.01)	0.110	
	14 – 19.9%	143831	1.00 (1.00-1.01)	0.573	
	< 14%	269240	-	-	
Distance	<= 5 miles	204454	0.95 (0.95-0.96)	**<.001**	**<.001**
	5 - 10 miles	156113	0.96 (0.96-0.97)	**<.001**	
	10 - 15 miles	85188	0.97 (0.96-0.97)	**<.001**	
	> 15 miles	167123	-	-	
Charlson-Deyo Score	0	523361	1.04 (1.02-1.06)	**<.001**	**<.001**
	1	74572	1.02 (1.00-1.04)	0.130	
	2	14945	-	-	
Pathologic T	T1	516779	1.05 (1.01-1.09)	**0.010**	**<.001**
	T2	92654	1.03 (0.99-1.07)	0.135	
	T3	3445	-	-	
Pathologic N	N0	443512	0.96 (0.95-0.97)	**<.001**	**<.001**
	N1	70053	0.92 (0.91-0.93)	**<.001**	
	N2	11361	0.89 (0.87-0.91)	**<.001**	
	NX	87952	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**

* Number of observations in the original data set = 612878. Number of observations used = 612878.
** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Median Income Quartiles 2000, and Urban/Rural 2003.

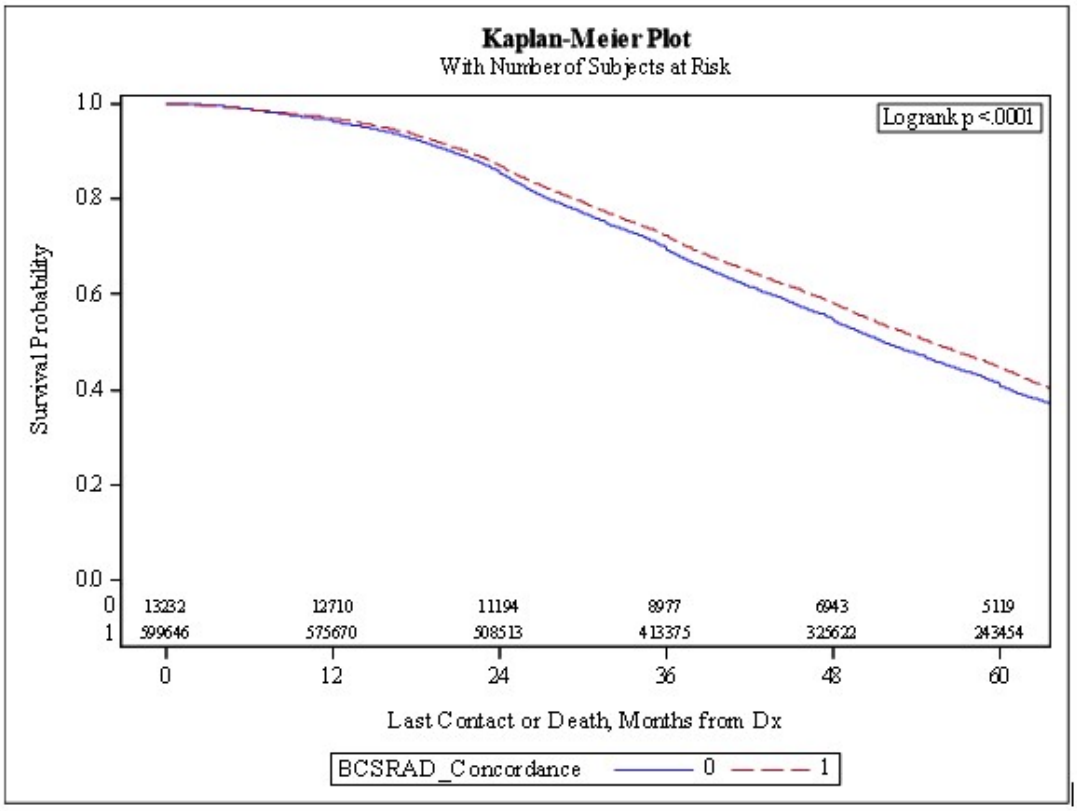


Figure 3: Kaplan Meier Curve for Receipt of Post-Breast Conserving Surgery Radiation Therapy

Chemotherapy

Cytotoxic chemotherapy has been used to treat breast cancer since the 1960's, with targeted therapy coming into widespread use beginning in the 1990's. Use of chemotherapy following surgery, when no clinical or radiological evidence of disease is observed, is termed *adjuvant* therapy and has been used since 1980's. Use of chemotherapy **prior to surgery**, or *neo-adjuvant* therapy, is more recent. Today, an extensive variety of drugs, combination regimens, doses, and schedules are approved for use as adjuvant and neo-adjuvant chemotherapy for early stage breast cancer.

Since 2010, NCCN guidelines have assigned appropriate regimens by HER-2 and hormone receptor (HR) status.

- For HER2+/HR+, HER2+/HR-, and HER2-/HR- cancers: chemotherapy is required if
    - Positive nodes OR
    - Primary cancer was greater than 1 cm.
- For HER2-/HR+ cancers: chemotherapy was required if there were positive nodes or if primary cancer was greater than 0.5 cm with a high recurrence score in the 21-gene RT-PCR assay.
    - Since the NCDB does not include this assay result, our study was unable to assess the latter criteria.

Chemotherapy Receipt from 2010 - 2013

A total of 435,389 patients were included in this study; overall chemotherapy compliance was 93.4%. There were 17369 HER2+/HR- breast cancer patients with 86.6% compliance. There were 39471 HER2+/HR+ breast cancer patients with 81.8% compliance. There were 328,485 HER2-/HR+ patients with 97.3% compliance. There were 50,064 HER2-/HR- patients with 83.2% compliance. Median age of

patient population was 58 years old. Median follow-up was 36 months. Baseline characteristics and unadjusted outcomes between eligible patients who received chemotherapy and those who did not are reported in **Table 6**. Selection criteria are seen in **Figure 4**.

Factors Associated with Chemotherapy Receipt for HER2+/HR- Patient

There was greater use of chemotherapy in eligible patients in integrated network cancer programs (86.9%) and academic/research programs (88.3%) compared to community cancer programs (82.9%) and comprehensive community cancer programs (86.1%). Patients living in the Northeast were the most likely to receive chemotherapy, while patients in the South were less likely to receive chemotherapy. Other factors that improved the chance of treatment include being less than 65, being black, having private insurance, earning greater than $46,000 a year, living in an area with greater than 83% high school graduation rate, living in a metro area, having a comorbidity score of 0, having a T1 or N0 pathologic staging, and being diagnosed in 2011 (**Table 7**).

On MVA (**Table 8**), receipt of chemotherapy in eligible HER2+/HR- patients was significantly associated with type of facility (p = <0.0001). Concordant patients were more likely to be in integrated network cancer programs compared to nonconcordant patients. Age was also a major determining factor for receipt of chemotherapy. Patients younger than 65 (OR 3.51 95% CI 3.31-3.71) and between 65-75 (OR 8.03 95% CI 7.5-8.64) were more likely to be concordant compared to patients greater than 75 years of age. Insurance status was also associated with chemotherapy receipt. Patients with government insurance (OR .70 95% CI 0.65 – 0.74) and non-insured patients (OR 0.72 95% CI 0.61 – .56) were less likely to receive chemotherapy compared to private insurance. Patients living in urban settings were more likely to receive chemotherapy compared to patients living in metro areas (OR 0.91 95% CI (.84-.97)). However, patients living in rural settings were more likely to receive chemotherapy compared to the urban setting (OR 1.19 95% CI (.99-1.43)).

Patient with lower comorbidities (Charlson Deyo scores of 0 and 1) were associated with higher rates of compliance compared to patients with high comorbidities (Charlson Deyo score of 2). In addition, patients with early N and T staging were more likely to be compliant compared to patients with later staging.

Factors Associated with Chemotherapy Receipt for HER2-/HR+ Patient

Baseline characteristics and unadjusted outcomes between eligible patients who received chemotherapy and those who did not are reported in **Table 11**. The highest rate of compliance was seen in academic/research programs (97.1%) and the Northeast region (97.5%). It is noted that geographically, while the West was the least compliant region, overall compliance was still 97%. Other variables associated with increased compliance include being less than 65 years of age, belonging to a racial group other than white or black, having private insurance, earning more than $46,000 a year, living in an area with greater than 83% high school graduation rate, having a Charlson Deyo score of 0, and having a T1 or N0 staging (**Table 12**).

On MVA (**Table 13**), geographic location showed a significant association in concordant rates in patients with early stage HER2-/HR+ breast cancer. Patients were significantly more likely to receive treatment in facilities in the Midwest (OR 1.19 CI 1.10-1.28), the Northeast (OR 1.14 CI 1.06 – 1.24), and the South (OR 1.11 CI 1.04 – 1.19) compared to the West.

Patients who were older received less guideline concordant chemotherapy compared to younger patients. Patients greater than 75 years old were less likely to receive appropriate chemotherapy compared to patients who were 65-75 years old (OR 3.51 CI 3.31 – 3.71) and patients who were less than 65 (OR 8.03 CI 7.5 – 8.64). Insurance status was also significant for guideline concordance. Government-insured and non-insured patients were less likely to be chemotherapy

concordant compared to patients with private insurance (OR 0.72 CI 0.61 – 0.86 and OR 0.72 CI 0.61 – 0.86, respectively).

Patient comorbidity status was also significantly associated with chemotherapy guideline concordance. Patients with a Charlson-Deyo score of 0 (OR 1.48 CI 1.33 – 1.64) and 1 (OR 1.37 CI 1.22-1.54) had higher odds of chemotherapy guideline concordance compared to patients with a Charlson-Deyo score of 2. Higher pathologic T and N staging also resulted in less chemotherapy administration in eligible patients.

Factors Associated with Chemotherapy Receipt for HER2+/HR+ Patient

Baseline characteristics and unadjusted outcomes between eligible patients who received chemotherapy and those who did not are reported in **Table 16**. On UVA, academic/research programs and integrated network cancer programs had the highest rates of compliance. Other factors associated with treatment include location in the Midwest, being less than 65 years of age, being a race other than white or black, having private insurance, earning more than $46,000 a year, residence in a zip code with greater than 83% high school graduation rate, being treated at a center greater than 15 miles away, having a Charlson Deyo score of 0, and having a pathologic T1 or N0 staging (**Table 17**).

On MVA, both facility type and facility location were significantly associated with receipt of chemotherapy. Patients who were concordant were more likely to be treated at integrated network cancer programs and academic research programs compared to nonconcordant patients. Geographically, facilities in the Midwest and Northeast had the greatest percentages of concordance, followed by the South and the West (**Table 18**).

Age and insurance also had significant associations in guideline concordance. Patients greater than 75 years old were less likely to be concordant compared to patients who were 65-75 years old (OR 4.2 CI 4.0 – 4.60) and less than 65 years old (OR 7.6 CI 6.9 – 8.3). Patients with government insurance

(OR .78 CI 0.73 – 0.83) and non-insured patients (OR 0.78 CI 0.64 – 0.96) were less likely to receive chemotherapy compared to private insurance.

Patients with pathologic stage T1 were more guideline concordant compared to T3 (OR 1.29 CI 1.08 – 1.55). Patients with unknown pathologic N stage were less likely to be concordant compared to patients staged N0 (OR 2.15 CI 1.92 – 2.40) or N1 (OR 3.59 CI 3.15 – 4.09). In addition, patients who were staged at T1 received treatment at a higher rate compared to patients staged at T3 (OR 1.29 CI 1.08-1.55). More recent year of diagnosis resulted in higher rates of compliance as well.

Factors Associated with Chemotherapy Receipt for Triple Negative Patients

Similar trends existed on UVA for triple negative patients. Baseline characteristics and unadjusted outcomes between eligible patients who received chemotherapy and those who did not are reported in **Table 21**. Specifically, patients in academic/research and integrated network cancer programs, were from the Northeast, were less than 65 years old, were a race other than white or black, had private insurance, earned greater than $46,000 a year, lived in a zip code with greater than 83% high school graduation rate, had a Charlson-Deyo score of 0, and were diagnosed in T1 or N0 pathologic stages on UVA (**Table 22**).

On MVA, patients who lived in the Midwest had the highest rate of concordance while patients in the West had the lowest rate of chemotherapy concordance. Academic/research programs and integrated network cancer programs had the highest odds of guidelines concordance compared to community cancer programs (OR 0.69 CI 0.61 – 0.78) and comprehensive community cancer programs (OR 0.85 CI 0.78 – 0.94) (**Table 23**).

Patients who are younger had higher odds of concordance compared to older patients. Patients who were less than 65 years old and patients who were 65-75 years of age had higher chemotherapy

administration compared to patients who were 75 years or older (OR 7.6 CI 6.9-8.3 and OR 4.2 CI 4.00-4.60, respectively).

Insurance was also associated with concordance. Patients with government insurance had significantly lower odds of concordance compared to patients with private insurance (OR 0.78 CI 0.64 – 0.96). Patient comorbidity status was also a significant factor associated with chemotherapy guideline concordance. Charlson-Deyo scores of 0 (OR 1.6 CI 1.4 – 1.8) and 1 (OR 1.5 CI 1.3-1.7) had higher odds of chemotherapy guideline concordance compared to patients with a Charlson-Deyo score of 2. Higher pathologic T staging also resulted in less chemotherapy administration in eligible patients. Patients with T1 (OR 1.29 CI 1.08 – 1.55) were more likely to receive chemotherapy compared to T3 patients. Patients diagnosed in 2010 were less like to be compliant compared to patient diagnosed in 2013 (OR 0.8 CI 0.74-0.86).

Impact of Chemotherapy on OS

Among HER2+/HR- patients who did not receive chemotherapy, the 3-year overall survival rate was 82.8% compared to 95.3% for patients who did receive chemotherapy (P<.001). Univariate survival (**Table 9**) analyses demonstrate that noncompliance led to a HR of 0.30 (95% CI 0.29-0.32). On MVA (**Table 10**), additional factors found to be associated with improved OS included being black (versus other non-white races), having a N staging of N2 (versus N0), and year of diagnosis. Adjusted HR in noncompliant patients versus compliant patients was 0.77 (95% CI 0.71-0.83). Kaplan Meier Curve is shown (**Figure 5**).

For HER2-/HR+ patients, the 3-year OS rate was 85.2% in noncompliant patients compared to 95.3% for compliant patients (P<.001). Univariate survival analyses demonstrate that noncompliance led to a HR of 0.31 (95% CI 0.29-0.33) (**Table 14**). On MVA (**Table 15**), additional factors found to be associated with improved OS included being treated at an integrated network cancer program, not

being treated in the South, being younger than 75 years of age, being white or black (versus other), having government or private insurance (versus not insured), having an earlier pathologic N staging, and living less than 15 miles away from the treatment center. Adjusted HR in noncompliant patients versus compliant patients was 0.76 (95% CI 0.71-0.80). Kaplan Meier Curve is shown (**Figure 6**).

Three-year OS rate for noncompliant HER2+/HR+ patients was 87.5% versus 96.8% for compliant patients (P<.001) (**Figure 7**). Unadjusted survival analyses demonstrated a HR of 0.26 (95% CI 0.23-0.29) for treatment compliance (**Table 19**). On MVA, factors associated with improved survival included being 75 years old or less (versus being older than 75), private insurance (versus government insurance or no insurance), having a Charlson-Deyo score of 0 and 1 (versus 2), being treated at a facility 15 miles or less (versus greater than 15 miles), being diagnosed in 2013 (versus 2010), having a staging of T1 and T2 (versus T3), and having a pathologic N0 and N1 stage (versus unknown staging). Adjusted HR is 0.5 (95% CI 0.43-0.56) (**Table 20**).

Among triple negative patients, 3-year OS survival was 85.2% for compliant patients and 75.4% for noncompliant patients (P<.001) (**Figure 8**). Unadjusted survival analyses demonstrated a HR of 0.37 (95% CI 0.34-0.38) (**Table 24**). On MVA, factors associated with improved overall survival included being 75 years old or less (versus being older than 75), being white and other (versus black), private insurance (versus government insurance or no insurance), having a Charlson-Deyo score of 0 and 1 (versus 2) being treated at a facility 15 miles away or less (versus greater than 15 miles), being diagnosed in 2013 (versus 2010), having a staging of T1 and T2 (versus T3), and having a pathologic N0 stage (versus unknown staging). Adjusted HR for significant variables was 0.5 (95% CI 0.45-0.52) (**Table 25**).

Discussion

The purpose of this investigation is to determine the facility, clinical, and socioeconomic factors that were associated with chemotherapy receipt for patients with early-stage breast cancer from 2010 –

2014. Overall, the rate of compliance was 93.4%. This is within the reported rates from other concordance studies, which ranged from 63.4% to 95.9% [57, 58]. Patients with HER2+/HR+ breast cancer had the lowest rate of compliance at 81.77%, while patients with HER2-/HR+ breast cancer had the highest rate of compliance, at 97.26%. The high rate of compliance for the HER2-/HR+ breast may be due to the fact that the majority of these cancers were treated with systemic endocrine treatments only. In addition, the NCCN incorporated 21 gene RT-PCR testing into its decision tree, a factor that the NCDB did not collect in the data available, and therefore we were unable to incorporate into our study.

We found that older patients, particularly those greater than 75 years of age, were less likely to receive guideline-concordant chemotherapy compared to patients who were younger. This trend has been reported in other studies [78-80]. These results might be due to confounding, as older patients may have higher comorbidities and worse tumor characteristics. While we adjusted for multiple variables, the results from our model may still suffer from residual confounding. Nonetheless, it is important that particular guidance and attention be given to older patients in order to make sure that they are offered the correct chemotherapy regimen and explicit or implicit bias does not impact clinical decision-making related to age alone.

Surprisingly, our data indicated that race/ethnicity was not a significant factor in determining guideline-concordant cancer care. The literature on the effect of race/ethnicity on chemotherapy is somewhat limited, and there are conflicting reports regarding whether race is a significant factor or not [54, 57, 81, 82]. Controlling for race reveals that more often it is a question of access – insurance, income, or education – that leads to disparities, rather than race or ethnicity alone.

Facility level factors also played a role in chemotherapy concordance. Lower volume institutions such as community cancer centers and comprehensive community cancer programs were less likely to adhere to guideline concordant therapy. This has also been observed in another study [57]. In addition,

facilities in the West consistently had the lowest rates of guideline concordance chemotherapy care. There is limited literature on the impact of geography on guideline concordance; most of the studies have only examined the issues regionally or compared between several states or institutions [55, 58, 83]. More studies are needed to examine this relationship on a national scale. But it is hypothesized that patients living in the West may encounter considerable distance in order to receive recommended chemotherapy.

Lower use of guideline-concordant chemotherapy among patients without private insurance is documented in numerous studies [57, 84]. It has been shown that Medicaid-insured women are more likely to have more comorbidities and have advanced disease [85], but the discrepancies in treatment still exists after adjusting for this in our analysis. One potential explanation for this is that there are additional underlying factors associated with not having private insurance, such as poor family support and/or less personal physician interaction, that are not directly accounted for in our analysis.

Concordance with chemotherapy in eligible patients resulted in a significant risk reduction in mortality. This is a different conclusion from the study conducted from van de Water et al., which did not show any significant association of chemotherapy receipt with overall survival [79]. However, this study was conducted in the Netherlands. The literature regarding chemotherapy concordance and survival is sparse and, to our knowledge, this is the first study that used the NCDB to examine this question. More studies should be conducted to confirm our results, but there are similar improvements in overall survival for patients who are adherent to guidelines concordant care in other systemic treatments for breast cancer [71].

This study has several limitations. The NCDB does not code for specific chemotherapy regimens, not does it code for the overall chemotherapy course. Therefore, we could only determine whether chemotherapy was initiated or not; it is not possible to evaluate whether any chemotherapy regimen

was completed as recommended. In addition, NCCN guidelines recommend the use of 21-RT PCR analysis in the determination of chemotherapy for patients with HER2-/HR+ disease; the NCDB did not record this information through 2013 so we were unable to account for this variable. We chose to categorize patients as being concordant or not based solely on receipt of chemotherapy, so these patients were considered nonconcordant without knowing if the gene assay might have indicated that chemotherapy should not be recommended. In addition, patients may have been categorized as 'non-concordant' but who may not have received chemotherapy due to personal preference or other medical reasons.

Strength of this study included its nationally representative and large sample size. The NCDB also codes for socioeconomic, facility, and patient characteristics that are not found in other databases of similar size. This allowed us to examine important variables that would be associated with guideline concordant chemotherapy and identify patients with characteristics that would place them at risk for not receiving the care that they needed. Targeting these patients specifically will ensure that they are not lost to follow-up.

Chemotherapy Figures

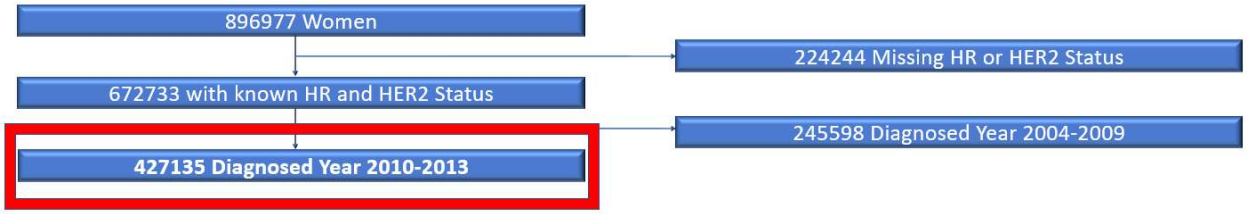


Figure 4: Selection Criteria for Chemotherapy

Table 6: Base Characteristics and Unadjusted Outcomes between Eligible Patients with HER2+/HR- Chemotherapy

Variable	Level	N (%) = 17396
Receipt of Chemotherapy	No	2331 (13.4)
	Yes	15065 (86.6)
Facility Type	Community Cancer Program/Other	1820 (10.5)
	Comprehensive Community Cancer Program	8123 (46.7)
	Academic/Research Program	5485 (31.5)
	Integrated Network Cancer Program	1968 (11.3)
Facility Location	Northeast	3646 (21.0)
	South	6578 (37.8)
	Midwest	4502 (25.9)
	West	2670 (15.3)
Age at Diagnosis (C)	<65	9398 (54.0)
	65-75	6053 (34.8)
	>75	1945 (11.2)

Variable	Level	N (%) = 17396
Race	White	13918 (80.0)
	Black	2396 (13.8)
	Other	1082 (6.2)
Insurance Type	Not Insured	409 (2.4)
	Private Insurance	9879 (56.8)
	Government Insurance	7108 (40.9)
Median Income Quartiles 2000	< $30,000	1980 (11.4)
	$30,000 - $35,999	2820 (16.2)
	$36,000 - $45,999	4683 (26.9)
	$46,000 +	7913 (45.5)
Percent No High School Degree Quartiles 2000	>= 29%	2740 (15.8)
	20 – 28.9%	3673 (21.1)
	14 – 19.9%	3978 (22.9)
	< 14%	7005 (40.3)
Urban/Rural 2003	Metro	14857 (85.4)
	Urban	2243 (12.9)
	Rural	296 (1.7)
Distance	<= 5 miles	5216 (30.0)
	5 - 10 miles	4232 (24.3)
	10 - 15 miles	2464 (14.2)
	> 15 miles	5484 (31.5)

Variable	Level	N (%) = 17396
Charlson-Deyo Score	0	14639 (84.2)
	1	2279 (13.1)
	2	478 (2.7)
Pathologic T	T1	12282 (70.6)
	T2	4546 (26.1)
	T3	568 (3.3)
Pathologic N	N0	12215 (70.2)
	N1	3314 (19.1)
	N2	1088 (6.3)
	NX	779 (4.5)
Year of Diagnosis	2009	487 (2.8)
	2010	3910 (22.5)
	2011	4165 (23.9)
	2012	4271 (24.6)
	2013	4563 (26.2)

Table 7: Univariate Association with Chemotherapy HER2+/HR- Patients

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =2331**	**Yes (%) =15065**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	311 (13.3)	1509 (10.0)	**<.001**
	Comprehensive Community Cancer Program	1123 (48.2)	7000 (46.5)	
	Academic/Research Program	641 (27.5)	4844 (32.2)	
	Integrated Network Cancer Program	256 (11.0)	1712 (11.4)	
Facility Location	Northeast	448 (19.2)	3198 (21.2)	0.062
	South	930 (39.9)	5648 (37.49)	
	Midwest	591 (25.4)	3911 (26.0)	
	West	362 (15.5)	2308 (15.3)	
Age at Diagnosis (C)	<65	698 (29.9)	8700 (57.7)	**<.001**
	65-75	819 (35.1)	5234 (34.7)	
	>75	814 (34.9)	1131 (7.5)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =2331**	**Yes (%) =15065**	**Parametric P-value***
Race	White	1898 (81.4)	12020 (79.8)	0.053
	Black	313 (13.4)	2083 (13.8)	
	Other	120 (5.2)	962 (6.4)	
Insurance Type	Not Insured	46 (2.0)	363 (2.41)	**<.001**
	Private Insurance	820 (35.2)	9059 (60.13)	
	Government Insurance	1465 (62.9)	5643 (37.5)	
Median Income Quartiles 2000	1	303 (13.0)	1677 (11.1)	**<.001**
	2	402 (17.3)	2418 (16.0)	
	3	665 (28.5)	4018 (26.7)	
	4	961 (41.2)	6952 (46.2)	
Percent No High School Degree Quartiles 2000	1	384 (16.5)	2356 (15.6)	**0.036**
	2	521 (22.4)	3152 (20.9)	
	3	551 (23.6)	3427 (22.8)	
	4	875 (37.5)	6130 (40.7)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =2331**	**Yes (%) =15065**	**Parametric P-value***
Urban/Rural 2003	Metro	1971 (84.6)	12886 (85.5)	0.431
	Urban	320 (13.7)	1923 (12.8)	
	Rural	40 (1.7)	256 (1.7)	
Distance	<= 5 miles	756 (32.4)	4460 (29.6)	**0.022**
	5 - 10 miles	572 (24.5)	3660 (24.3)	
	10 - 15 miles	312 (13.4)	2152 (14.3)	
	> 15 miles	691 (29.6)	4793 (31.8)	
Charlson-Deyo Score	0	1867 (80.1)	12772 (84.8)	**<.001**
	1	348 (14.9)	1931 (12.8)	
	2	116 (5.0)	362 (2.4)	
Pathologic T	T1	1527 (65.5)	10755 (71.4)	**<.001**
	T2	708 (30.4)	3838 (25.5)	
	T3	96 (4.1)	472 (3.1)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =2331**	**Yes (%) =15065**	**Parametric P-value***
Pathologic N	N0	1641 (70.4)	10574 (70.2)	**<.001**
	N1	317 (13.6)	2997 (19.9)	
	N2	100 (4.3)	988 (6.6)	
	NX	273 (11.7)	506 (3.4)	
Year of Diagnosis	2009	50 (2.2)	437 (2.9)	**0.030**
	2010	519 (22.3)	3391 (22.5)	
	2011	534 (22.9)	3631 (24.1)	
	2012	564 (24.2)	3707 (24.61	
	2013	664 (28.5)	3899 (25.9)	

* The parametric p-value is calculated by chi-square test. Percentage calculated within each individual category.

Table 8: Multivariable Logistic Regression Model for HER2+/HR- Chemotherapy

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Facility Type	Community Cancer Program/Other	0.72 (0.50-0.88)	**<.001**	**0.0003**
	Comprehensive Community Cancer Program	0.98 (0.84-1.15)	.08	
	Academic/Research Program	1.01 (0.85-1.20)	**.03**	
	Integrated Network Cancer Program	-	-	
Facility Location	Northeast	1.19 (1.01-1.41)	**.037**	**0.0162**
	South	1.0 (0.86-1.15)	**.032**	
	Midwest	1.15 (0.99-1.35)	.14	
	West	-	-	
Age at Diagnosis (C)	<65	6.76 (5.83-7.83)	**<.001**	**<.0001**
	65-75	4.15 (3.66-4.69)	**<.001**	
	>75	-	-	
Insurance Type	Not Insured	0.73 (0.53-1.01)	0.34	**<.0001**
	Government Insurance	0.73 (0.65-0.83)	0.10	
	Private Insurance	-	-	

		Receipt of Chemotherapy		

Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Percent No High School Education	20%-29.0%	0.80 (0.76-0.85)	**<.001**	
	14%–19.9%	0.91 (0.87-0.96)	**0.002**	
	< 14%	-	-	
Charlson-Deyo Score	0	1.56 (1.24-1.98)	**.001**	**0.001**
	1	1.53 (1.18-1.98)	**0.02**	
	2	-	-	
Pathologic N	N0	2.99 (2.52-3.55)	**<.001**	**<.0001**
	N1	5.33 (4.33-6.57)	**<.001**	
	N2	5.99 (4.53-7.90)	**<.001**	
	NX	-	-	

Table 9: Univariate Association with Overall Survival for HER2+/HR- Chemotherapy

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	17396	0.25 (0.22-0.29)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	1820	1.03 (0.96-1.10)	0.388	**0.022**
	Comprehensive Community Cancer Program	8123	0.99 (0.94-1.04)	0.684	
	Academic/Research Program	5485	1.04 (0.99-1.10)	0.113	
	Integrated Network Cancer Program	1968	-	**-**	
Facility Location	Northeast	3646	0.99 (0.94-1.04)	0.727	0.910
	South	6578	0.99 (0.94-1.04)	0.628	
	Midwest	4502	1.00 (0.95-1.05)	0.956	
	West	2670	-	**-**	
Age at Diagnosis (C)	<65	9398	0.95 (0.90-1.01)	0.100	**0.001**
	65-75	6053	1.02 (0.96-1.07)	0.604	
	>75	1945	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Race	White	13918	0.96 (0.90-1.02)	0.218	0.375
	Black	2396	0.95 (0.88-1.02)	0.166	
	Other	1082	-	-	
Insurance Type	Not Insured	409	1.06 (0.96-1.18)	0.263	**<.001**
	Private Insurance	9879	0.95 (0.92-0.98)	**<.001**	
	Government Insurance	7108	-	-	
Median Income Quartiles 2000	< $30,000	1980	0.98 (0.93-1.03)	0.398	0.639
	$30,000 - $35,999	2820	0.99 (0.95-1.04)	0.671	
	$36,000 - $45,999	4683	0.98 (0.94-1.02)	0.239	
	$46,000 +	7913	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	2740	1.00 (0.95-1.04)	0.882	0.959
	20 – 28.9%	3673	0.99 (0.95-1.03)	0.580	
	14 – 19.9%	3978	1.00 (0.96-1.04)	0.843	
	< 14%	7005	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	14857	1.00 (0.89-1.13)	0.963	0.991
	Urban	2243	1.01 (0.89-1.14)	0.929	
	Rural	296	-	-	
Distance	<= 5 miles	5216	0.96 (0.92-1.00)	**0.044**	0.135
	5 - 10 miles	4232	0.98 (0.94-1.03)	0.436	
	10 - 15 miles	2464	0.96 (0.91-1.00)	0.067	
	> 15 miles	5484	-	-	
Charlson-Deyo Score	0	14639	0.97 (0.87-1.07)	0.517	0.724
	1	2279	0.98 (0.88-1.09)	0.703	
	2	478	-	-	
Pathologic T	T1	12282	1.20 (1.09-1.31)	**<.001**	**<.001**
	T2	4546	1.11 (1.01-1.22)	**0.038**	
	T3	568	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	12215	0.96 (0.89-1.04)	0.334	**<.001**
	N1	3314	0.89 (0.82-0.96)	**0.005**	
	N2	1088	0.80 (0.73-0.89)	**<.001**	
	NX	779	-	**-**	
Year of Diagnosis	2009	487	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	3910	0.00 (0.00-0.01)	**<.001**	
	2011	4165	0.03 (0.03-0.03)	**<.001**	
	2012	4271	0.17 (0.16-0.18)	**<.001**	
	2013	4563	-	**-**	

Table 10: Multivariable Cox Proportional Hazard Model for Overall Survival for HER2+/HR- Chemotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	17396	0.41 (0.36-0.48)	**<.001**	**<.001**
Facility Location	Northeast	3646	1.05 (1.00-1.11)	0.053	0.056
	South	6578	1.05 (1.00-1.10)	0.051	
	Midwest	4502	1.01 (0.96-1.06)	0.756	
	West	2670	-	-	
Race	White	13918	0.99 (0.93-1.05)	0.736	**0.024**
	Black	2396	0.93 (0.86-1.00)	0.055	
	Other	1082	-	-	
Insurance Type	Not Insured	409	1.10 (0.99-1.22)	0.072	0.145
	Private Insurance	9879	0.99 (0.96-1.03)	0.662	
	Government Insurance	7108	-	-	
Distance	<= 5 miles	5216	0.97 (0.94-1.01)	0.206	0.053
	5 - 10 miles	4232	0.97 (0.93-1.01)	0.183	
	10 - 15 miles	2464	0.93 (0.89-0.98)	**0.006**	
	> 15 miles	5484	-	-	
Pathologic N	N0	12215	0.97 (0.90-1.05)	0.443	**0.015**
	N1	3314	0.93 (0.86-1.02)	0.110	
	N2	1088	0.88 (0.80-0.98)	**0.017**	
	NX	779	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Year of Diagnosis	2009	487	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	3910	0.00 (0.00-0.01)	**<.001**	
	2011	4165	0.03 (0.03-0.03)	**<.001**	
	2012	4271	0.17 (0.16-0.18)	**<.001**	
	2013	4563	-	-	

* Number of observations in the original data set = 17396. Number of observations used = 17396.
** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Age at Diagnosis (C), Charlson-Deyo Score, Facility Type, Median Income Quartiles 2000, Percent No High School Degree Quartiles 2000, Pathologic T, and Urban/Rural 2003.

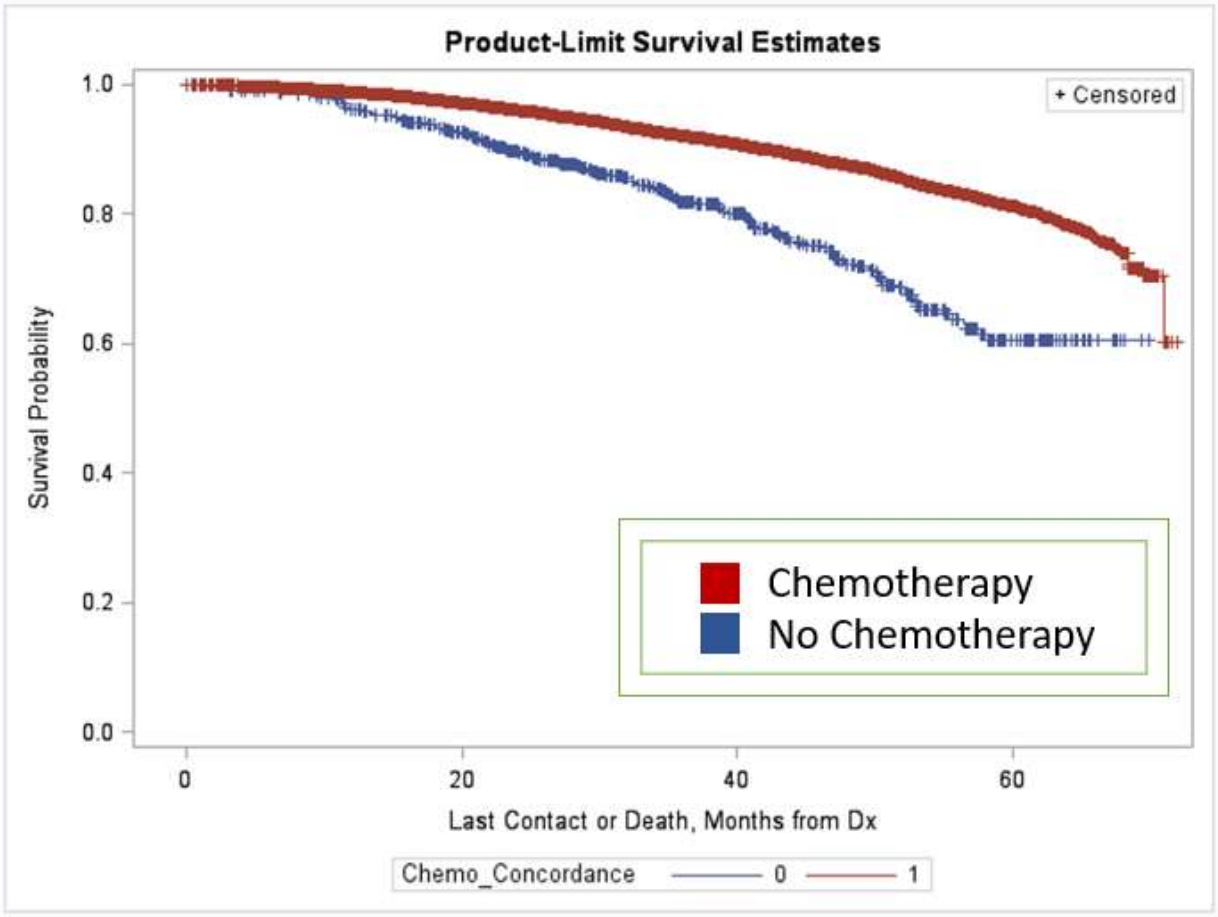


Figure 5: Kaplan Meier Curve for HER2+/HR- Breast Cancer

Table 11: Descriptive Statistics for All Variables for HER2-/HR+ Chemotherapy

Variable	Level	N (%) = 328485
Chemotherapy Receipt	No	9008 (2.7)
	Yes	319477 (97.3)
Facility Type	Community Cancer Program/Other	34967 (10.6)
	Comprehensive Community Cancer Program	158312 (48.2)
	Academic/Research Program	98619 (30.0)
	Integrated Network Cancer Program	36587 (11.1)
Facility Location	Northeast	71695 (21.8)
	South	114266 (34.8)
	Midwest	85504 (26.0)
	West	57020 (17.4)
Age at Diagnosis (C)	<65	132920 (40.5)
	65-75	137778 (41.9)
	>75	57787 (17.6)
Race	White	285764 (87.0)
	Black	29696 (9.0)
	Other	13025 (4.0)
Insurance Type	Not Insured	5288 (1.6)
	Private Insurance	161725 (49.2)
	Government Insurance	161472 (49.2)

Variable	Level	N (%) = 328485
Median Income Quartiles 2000	< $30,000	32444 (9.9)
	$30,000 - $35,999	50847 (15.5)
	$36,000 - $45,999	88041 (26.8)
	$46,000 +	157153 (47.8)
Percent No High School Degree Quartiles 2000	>= 29%	42472 (12.9)
	20 – 28.9%	66836 (20.3)
	14 – 19.9%	76845 (23.4)
	< 14%	142332 (43.3)
Urban/Rural 2003	Metro	280027 (85.2)
	Urban	42693 (13.0)
	Rural	5765 (1.8)
Distance	<= 5 miles	102288 (31.1)
	5 - 10 miles	81097 (24.7)
	10 - 15 miles	46232 (14.1)
	> 15 miles	98868 (30.1)
Charlson-Deyo Score	0	270892 (82.5)
	1	47068 (14.3)
	2	10525 (3.2)
Pathologic T	T1	242311 (73.8)
	T2	76803 (23.4)
	T3	9371 (2.9)

Variable	Level	N (%) = 328485
Pathologic N	N0	238192 (72.5)
	N1	61725 (18.8)
	N2	13688 (4.2)
	NX	14880 (4.5)
Year of Diagnosis	2009	6392 (1.9)
	2010	70941 (21.6)
	2011	79014 (24.1)
	2012	83338 (25.4)
	2013	88800 (27.0)

Table 12: Univariate Association with HER2-/HR+ Chemotherapy Receipt

Covariate	Level	Receipt of Chemotherapy: No (%) =9008	Receipt of Chemotherapy: Yes (%) =319477	Parametric P-value*
Facility Type	Community Cancer Program/Other	1059 (11.8)	33908 (10.6)	**<.001**
	Comprehensive Community Cancer Program	4444 (49.3)	153868 (48.2)	
	Academic/Research Program	2494 (27.7)	96125 (30.0)	
	Integrated Network Cancer Program	1011 (11.2)	35576 (11.1)	
Facility Location	Northeast	1745 (19.4)	69950 (21.9)	**<.001**
	South	3288 (36.5)	110978 (34.7)	
	Midwest	2291 (25.4)	83213 (26.0)	
	West	1684 (18.7)	55336 (17.3)	
Age at Diagnosis (C)	<65	1983 (22.0)	130937 (41.0)	**<.001**
	65-75	3557 (39.5)	134221 (42.0)	
	>75	3468 (38.5)	54319 (17.0)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =9008**	**Yes (%) =319477**	**Parametric P-value***
Race	White	7746 (86.0)	278018 (87.0)	**<.001**
	Black	976 (10.8)	28720 (9.0)	
	Other	286 (3.2)	12739 (4.0)	
Insurance Type	Not Insured	154 (1.7)	5134 (1.6)	**<.001**
	Private Insurance	2685 (29.8)	159040 (49.8)	
	Government Insurance	6169 (68.5)	155303 (48.6)	
Median Income Quartiles 2000	< $30,000	1109 (12.3)	31335 (9.8)	**<.001**
	$30,000 - $35,999	1500 (16.6)	49347 (15.5)	
	$36,000 - $45,999	2635 (29.3)	85406 (26.7)	
	$46,000 +	3764 (41.8)	153389 (48.0)	
Percent No High School Degree Quartiles 2000	>= 29%	1403 (15.6)	41069 (12.9)	**<.001**
	20 – 28.9%	2048 (22.7)	64788 (20.3)	
	14 – 19.9%	2093 (23.23)	74752 (23.4)	
	< 14%	3464 (38.5)	138868 (43.5)	

Covariate	Level	Receipt of Chemotherapy: No (%) =9008	Receipt of Chemotherapy: Yes (%) =319477	Parametric P-value*
Urban/Rural 2003	Metro	7625 (84.7)	272402 (85.3)	0.264
	Urban	1218 (13.5)	41475 (12.9)	
	Rural	165 (1.8)	5600 (1.7)	
Distance	<= 5 miles	2991 (33.2)	99297 (31.0)	**<.001**
	5 - 10 miles	2182 (24.2)	78915 (24.7)	
	10 - 15 miles	1147 (12.7)	45085 (14.1)	
	> 15 miles	2688 (29.8)	96180 (30.1)	
Charlson-Deyo Score	0	6786 (75.3)	264106 (82.7)	**<.001**
	1	1675 (18.6)	45393 (14.2)	
	2	547 (6.0)	9978 (3.1)	
Pathologic T	T1	3595 (39.9)	238716 (74.7)	**<.001**
	T2	4499 (49.9)	72304 (22.6)	
	T3	914 (10.2)	8457 (2.7)	

Covariate	Level	Receipt of Chemotherapy: No (%) =9008	Receipt of Chemotherapy: Yes (%) =319477	Parametric P-value*
Pathologic N	N0	109 (1.2)	238083 (74.5)	**<.001**
	N1	6544 (72.7	55181 (17.3)	
	N2	2339 (26.0)	11349 (3.6)	
	NX	16 (0.2)	14864 (4.6)	
Year of Diagnosis	2009	170 (1.9)	6222 (2.0)	0.100
	2010	2043 (22.7)	68898 (21.6)	
	2011	2167 (24.1)	76847 (24.0)	
	2012	2212 (24.6)	81126 (25.4)	
	2013	2416 (26.8)	86384 (27.0)	

* The parametric p-value is calculated by chi-square test. Percentages are calculated within category.

Table 13: Multivariable Logistic Regression Model for HR+ Chemotherapy

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Facility Location	Northeast	1.14 (1.06-1.24)	0.17	**<.0001**
	South	1.11 (1.04-1.19)	0.92	
	Midwest	1.19 (1.10-1.28)	**0.0013**	
	West	-	-	
Age at Diagnosis (C)	65 - 75	3.51 (3.31-3.71)	**<.001**	**<.0001**
	< 65	8.03 (7.5 -8.64)	**<.001**	
	>75	-	-	
Insurance Type	Not Insured	0.72 (0.61-0.86)	0.10	**<.0001**
	Government Insurance	0.70 (0.65-0.74)	**<0.001**	
	Private Insurance	-	-	
Urbanicity	Metro	0.91 (0.84-0.93)	**0.0008**	**.003**
	Rural	1.19 (0.99-1.43)	**0.01**	
	Urban	-	-	

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Charlson-Deyo Score	0	1.48 (1.33-1.64)	**<.0001**	**<0.001**
	1	1.37 (1.22-1.54)	**0.0021**	
	2	-	-	
Pathologic N	N0	1.25 (.74-2.2)	**<.001**	**<.0001**
	N1	0.004 (0.002-0.006)	**<.001**	
	N2	0.002 (0.001-0.004)	**<.001**	
	NX	-	-	
Pathologic T	T1	1.4 (1.3-1.5)	**<.001**	**<.0001**
	T2	1.08 (1.00-1.17)	**0.0003**	
	T3	-	**-**	

Table 14: Univariate Association with Overall Survival for HER2+/HR- Chemotherapy

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Receipt of Chemotherapy	Yes	328485	0.30 (0.29-0.32)	0.200	0.200
Facility Type	Community Cancer Program/Other	34967	1.01 (0.99-1.02)	0.223	**<.001**
	Comprehensive Community Cancer Program	158312	1.00 (0.99-1.02)	0.431	
	Academic/Research Program	98619	1.03 (1.02-1.05)	**<.001**	
	Integrated Network Cancer Program	36587	-	**-**	
Facility Location	Northeast	71695	1.01 (1.00-1.02)	0.160	**<.001**
	South	114266	0.98 (0.97-0.99)	**<.001**	
	Midwest	85504	0.99 (0.98-1.00)	0.098	
	West	57020	-	**-**	
Age at Diagnosis (C)	<65	132920	1.00 (0.99-1.01)	0.387	**<.001**
	65-75	137778	1.02 (1.01-1.03)	**<.001**	
	>75	57787	-	**-**	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Race	White	285764	0.93 (0.91-0.94)	**<.001**	**<.001**
	Black	29696	0.93 (0.91-0.95)	**<.001**	
	Other	13025	-	**-**	
Insurance Type	Not Insured	5288	1.06 (1.03-1.09)	**<.001**	**<.001**
	Private Insurance	161725	0.97 (0.97-0.98)	**<.001**	
	Government Insurance	161472	-	**-**	
Median Income Quartiles 2000	< $30,000	32444	0.98 (0.97-1.00)	**0.016**	0.092
	$30,000 - $35,999	50847	0.99 (0.98-1.00)	0.204	
	$36,000 - $45,999	88041	1.00 (0.99-1.01)	0.502	
	$46,000 +	157153	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	42472	1.00 (0.99-1.01)	0.661	0.186
	20 – 28.9%	66836	0.99 (0.98-1.00)	**0.039**	
	14 – 19.9%	76845	1.00 (0.99-1.01)	0.976	
	< 14%	142332	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	280027	1.03 (1.00-1.06)	**0.039**	0.057
	Urban	42693	1.03 (1.01-1.06)	**0.018**	
	Rural	5765	-	**-**	
Distance	<= 5 miles	102288	0.95 (0.94-0.96)	**<.001**	**<.001**
	5 - 10 miles	81097	0.97 (0.96-0.98)	**<.001**	
	10 - 15 miles	46232	0.98 (0.97-0.99)	**<.001**	
	> 15 miles	98868	-	**-**	
Charlson-Deyo Score	0	270892	0.96 (0.94-0.98)	**<.001**	**<.001**
	1	47068	0.98 (0.96-1.01)	0.142	
	2	10525	-	**-**	
Pathologic T	T1	242311	1.06 (1.04-1.09)	**<.001**	**<.001**
	T2	76803	1.03 (1.01-1.06)	**0.004**	
	T3	9371	-	**-**	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	238192	0.95 (0.93-0.97)	**<.001**	**<.001**
	N1	61725	0.91 (0.89-0.93)	**<.001**	
	N2	13688	0.83 (0.81-0.85)	**<.001**	
	NX	14880	-	**-**	
Year of Diagnosis	2009	6392	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	70941	0.00 (0.00-0.00)	**<.001**	
	2011	79014	0.03 (0.03-0.03)	**<.001**	
	2012	83338	0.17 (0.17-0.17)	**<.001**	
	2013	88800	-	**-**	

Table 15: Multivariate Cox Proportional Hazard Model for Overall Survival HER2-/HR+ Chemotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	328485	0.77 (0.71-0.83)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	34967	1.06 (1.04-1.07)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	158312	1.04 (1.03-1.05)	**<.001**	
	Academic/Research Program	98619	1.03 (1.02-1.05)	**<.001**	
	Integrated Network Cancer Program	36587	-	-	
Facility Location	Northeast	71695	1.01 (1.00-1.02)	0.103	**<.001**
	South	114266	1.02 (1.01-1.03)	**<.001**	
	Midwest	85504	0.99 (0.98-1.00)	0.050	
	West	57020	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Age at Diagnosis (C)	<65	132920	0.99 (0.97-1.00)	**0.027**	**0.002**
	65-75	137778	0.98 (0.97-0.99)	**<.001**	
	>75	57787	-	-	
Race	White	285764	0.96 (0.95-0.98)	**<.001**	**<.001**
	Black	29696	0.95 (0.93-0.97)	**<.001**	
	Other	13025	-	-	
Insurance Type	Not Insured	5288	1.09 (1.06-1.12)	**<.001**	**<.001**
	Private Insurance	161725	1.00 (0.99-1.01)	0.657	
	Government Insurance	161472	-	-	
Distance	<= 5 miles	102288	0.97 (0.96-0.98)	**<.001**	**<.001**
	5 - 10 miles	81097	0.97 (0.96-0.98)	**<.001**	
	10 - 15 miles	46232	0.98 (0.96-0.99)	**<.001**	
	> 15 miles	98868	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Charlson-Deyo Score	0	270892	1.02 (1.00-1.04)	**0.042**	**<.001**
	1	47068	1.00 (0.98-1.02)	0.918	
	2	10525	-	-	
Pathologic T	T1	242311	1.01 (0.99-1.04)	0.285	**0.023**
	T2	76803	1.00 (0.98-1.02)	0.985	
	T3	9371	-	-	
Pathologic N	N0	238192	0.95 (0.94-0.97)	**<.001**	**<.001**
	N1	61725	0.91 (0.89-0.93)	**<.001**	
	N2	13688	0.86 (0.84-0.88)	**<.001**	
	NX	14880	-	-	
Year of Diagnosis	2009	6392	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	70941	0.00 (0.00-0.00)	**<.001**	
	2011	79014	0.03 (0.03-0.03)	**<.001**	
	2012	83338	0.17 (0.17-0.17)	**<.001**	
	2013	88800	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**

* Number of observations in the original data set = 328485. Number of observations used = 328485.

** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the

model: Median Income Quartiles 2000, Percent No High School Degree Quartiles 2000, and Urban/Rural 2003.

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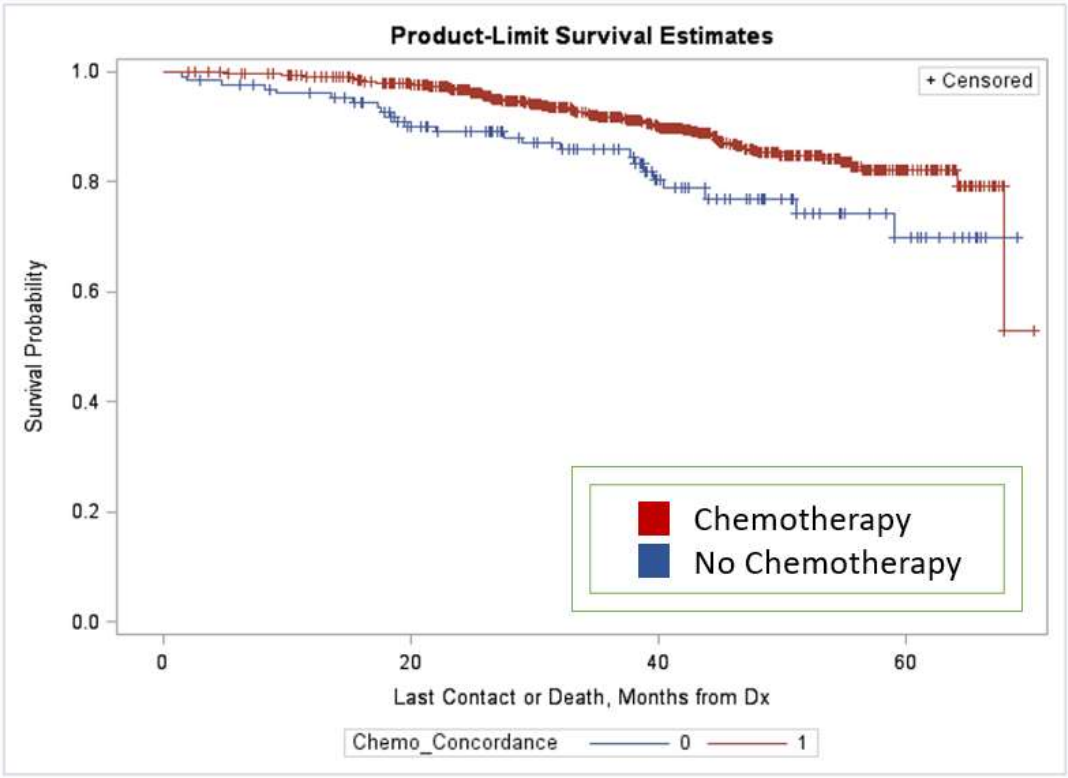


Figure 6: Kaplan Meier Curve for HER2-/HR+ Breast Cancer

Table 16: Descriptive Statistics for All Variables HER2+/HR+ Chemotherapy

Variable	Level	N (%) = 39471
Chemotherapy Receipt	No	7197 (18.2)
	Yes	32274 (81.8)
Facility Type	Community Cancer Program/Other	4445 (11.3)
	Comprehensive Community Cancer Program	18720 (47.4)
	Academic/Research Program	12048 (30.5)
	Integrated Network Cancer Program	4258 (10.8)
Facility Location	Northeast	8445 (21.4)
	South	14606 (37.0)
	Midwest	10141 (25.7)
	West	6279 (15.9)
Age at Diagnosis (C)	<65	21200 (53.7)
	65-75	13527 (34.3)
	>75	4744 (12.0)
Race	White	33083 (83.8)
	Black	4385 (11.1)
	Other	2003 (5.1)
Insurance Type	Not Insured	859 (2.2)
	Private Insurance	22509 (57.0)
	Government Insurance	16103 (40.8)

Variable	Level	N (%) = 39471
Median Income Quartiles 2000	< $30,000	4343 (11.0)
	$30,000 - $35,999	6255 (15.8)
	$36,000 - $45,999	10460 (26.5)
	$46,000 +	18413 (46.6)
Percent No High School Degree Quartiles 2000	>= 29%	5746 (14.6)
	20 – 28.9%	8340 (21.1)
	14 – 19.9%	9024 (22.9)
	< 14%	16361 (41.5)
Urban/Rural 2003	Metro	33555 (85.0)
	Urban	5209 (13.2)
	Rural	707 (1.8)
Distance	<= 5 miles	11855 (30.0)
	5 - 10 miles	9628 (24.4)
	10 - 15 miles	5677 (14.4)
	> 15 miles	12311 (31.2)
Charlson-Deyo Score	0	33190 (84.1)
	1	5221 (13.2)
	2	1060 (2.7)
Pathologic T	T1	27730 (70.3)
	T2	10714 (27.1)
	T3	1027 (2.6)

Variable	Level	N (%) = 39471
Pathologic N	N0	27365 (69.3)
	N1	8059 (20.4)
	N2	2287 (5.8)
	NX	1760 (4.5)
Year of Diagnosis	2010	8860 (22.4)
	2011	9635 (24.4)
	2012	10065 (25.5)
	2013	10911 (27.6)

Table 17: Univariate Association of HER2+/HR+ Chemotherapy

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =7197**	**Yes (%)=32274**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	1022 (14.2)	3423 (10.61)	**<.001**
	Comprehensive Community Cancer Program	3618 (50.3)	15102 (46.8)	
	Academic/Research Program	1851 (25.7)	10197 (31.6)	
	Integrated Network Cancer Program	706 (9.8)	3552 (11.0)	
Facility Location	Northeast	1473 (20.5)	6972 (21.6)	**<.001**
	South	2906 (40.4)	11700 (36.3)	
	Midwest	1661 (23.1)	8480 (26.3)	
	West	1157 (16.1)	5122 (15.9)	
Age at Diagnosis (C)	<65	2116 (29.4)	19084 (59.1)	**<.001**
	65-75	2580 (35.9)	10947 (33.9)	
	>75	2501 (34.8)	2243 (7.0)	

Covariate	Level	Receipt of Chemotherapy: No (%) =7197	Receipt of Chemotherapy: Yes (%)=32274	Parametric P-value*
Race	White	6097 (84.7)	26986 (83.6)	**<.001**
	Black	808 (11.2)	3577 (11.1)	
	Other	292 (4.0)	1711 (5.3)	
Insurance Type	Not Insured	121 (1.7)	738 (2.3)	**<.001**
	Private Insurance	2621 (36.4)	19888 (61.6)	
	Government Insurance	4455 (61.9)	11648 (36.1)	
Median Income Quartiles 2000	< $30,000	925 (12.9)	3418 (10.6)	**<.001**
	$30,000 - $35,999	1308 (18.2)	4947 (15.3)	
	$36,000 - $45,999	1934 (26.9)	8526 (26.4)	
	$46,000 +	3030 (42.1)	15383 (47.7)	
Percent No High School Degree Quartiles 2000	>= 29%	1208 (16.8)	4538 (14.1)	**<.001**
	20 – 28.9%	1671 (23.2)	6669 (20.7)	
	14 – 19.9%	1603 (22.3)	7421 (23.0)	
	< 14%	2715 (37.7)	13646 (42.3)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%) =7197**	**Yes (%)=32274**	**Parametric P-value***
Urban/Rural 2003	Metro	6043 (84.0)	27512 (85.3)	**0.022**
	Urban	1018 (14.1)	4191 (13.0)	
	Rural	136 (1.9)	571 (1.8)	
Distance	<= 5 miles	2455 (34.1)	9400 (29.1)	**<.001**
	5 - 10 miles	1739 (24.2)	7889 (24.4)	
	10 - 15 miles	951 (13.2)	4726 (14.6)	
	> 15 miles	2052 (28.5)	10259 (31.8)	
Charlson-Deyo Score	0	5655 (78.6)	27535 (85.3)	**<.001**
	1	1197 (16.6)	4024 (12.5)	
	2	345 (4.8)	715 (2.2)	
Pathologic T	T1	4842 (67.3)	22888 (70.9)	**<.001**
	T2	2173 (30.2)	8541 (26.5)	
	T3	182 (2.5)	845 (2.6)	

Covariate	Level	Receipt of Chemotherapy		Parametric P-value*
		No (%) =7197	Yes (%)=32274	
Pathologic N	N0	5212 (72.4)	22153 (68.6)	**<.001**
	N1	1070 (14.9)	6989 (21.7)	
	N2	221 (3.0)	2066 (6.4)	
	NX	694 (9.6)	1066 (3.3)	
Year of Diagnosis	2010	1794 (24.9)	7066 (21.9)	**<.001**
	2011	1760 (24.5)	7875 (24.4)	
	2012	1779 (24.7)	8286 (25.7)	
	2013	1864 (25.9)	9047 (28.0)	

* The parametric p-value is calculated by chi-square test. Percentage calculated within individual category.

Table 18: Multivariable Logistic Regression Model for HER2+/HR+ Chemotherapy

			Receipt of Chemotherapy		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Facility Type	Community Cancer Program/Other	4445	0.69 (0.61-0.78)	<.001	**<.001**
	Comprehensive Community Cancer Program	18720	0.85 (0.78-0.94)	0.001	
	Academic/Research Program	12048	0.94 (0.84-1.04)	0.211	
	Integrated Network Cancer Program	4258	-	-	
Facility Location	Northeast	8445	1.16 (1.06-1.28)	0.002	**<.001**
	South	14606	1.01 (0.93-1.10)	0.854	
	Midwest	10141	1.28 (1.17-1.40)	<.001	
	West	6279	-	-	
Age at Diagnosis (C)	<65	21200	7.62 (6.97-8.33)	<.001	**<.001**
	65-75	13527	4.26 (3.96-4.60)	<.001	
	>75	4744	-	-	

			Receipt of Chemotherapy		

Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Race	White	33083	0.97 (0.84-1.11)	0.651	0.081
	Black	4385	0.88 (0.75-1.03)	0.100	
	Other	2003	-	-	
Insurance Type	Not Insured	859	1.01 (0.82-1.23)	0.958	**<.001**
	Private Insurance	22509	1.29 (1.20-1.38)	<.001	
	Government Insurance	16103	-	-	
Median Income Quartiles 2000	< $30,000	4343	1.00 (0.88-1.13)	0.995	0.487
	$30,000 - $35,999	6255	0.95 (0.86-1.05)	0.325	
	$36,000 - $45,999	10460	1.02 (0.94-1.10)	0.641	
	$46,000 +	18413	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	5746	0.84 (0.75-0.94)	0.002	**0.003**
	20 – 28.9%	8340	0.87 (0.79-0.95)	0.002	
	14 – 19.9%	9024	0.97 (0.90-1.05)	0.478	
	< 14%	16361	-	-	

			Receipt of Chemotherapy		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	33555	0.98 (0.79-1.22)	0.888	0.979
	Urban	5209	0.98 (0.79-1.22)	0.849	
	Rural	707	-	-	
Distance	<= 5 miles	11855	0.93 (0.86-1.00)	0.059	0.310
	5 - 10 miles	9628	0.95 (0.88-1.03)	0.244	
	10 - 15 miles	5677	0.95 (0.87-1.05)	0.340	
	> 15 miles	12311	-	-	
Charlson-Deyo Score	0	33190	1.59 (1.38-1.84)	<.001	**<.001**
	1	5221	1.49 (1.28-1.74)	<.001	
	2	1060	-	-	
Pathologic T	T1	27730	1.29 (1.08-1.55)	0.006	**<.001**
	T2	10714	0.97 (0.81-1.17)	0.783	
	T3	1027	-	-	

			Receipt of Chemotherapy		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Pathologic N	N0	27365	2.15 (1.92-2.40)	<.001	**<.001**
	N1	8059	3.59 (3.15-4.08)	<.001	
	N2	2287	5.76 (4.79-6.94)	<.001	
	NX	1760	-	-	
Year of Diagnosis	2010	8860	0.80 (0.74-0.86)	<.001	**<.001**
	2011	9635	0.94 (0.87-1.02)	0.115	
	2012	10065	0.96 (0.89-1.04)	0.341	
	2013	10911	-	-	

* Number of observations in the original data set = 39471. Number of observations used = 39471.

** Backward selection with an alpha level of removal of .05 was used. No variables were removed from the model.

Table 19: Univariate Association with Overall Survival for HER2+/HR+ Chemotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	39471	0.26 (0.23-0.26)	0.300	**<.001**
Facility Type	Community Cancer Program/Other	4445	0.97 (0.93-1.02)	0.229	**<.001**
	Comprehensive Community Cancer Program	18720	0.97 (0.93-1.00)	0.051	
	Academic/Research Program	12048	1.01 (0.98-1.05)	0.418	
	Integrated Network Cancer Program	4258	-	-	
Facility Location	Northeast	8445	0.97 (0.94-1.01)	0.108	0.247
	South	14606	1.00 (0.97-1.03)	0.777	
	Midwest	10141	0.98 (0.95-1.01)	0.229	
	West	6279	-	-	
Age at Diagnosis (C)	<65	21200	1.01 (0.98-1.05)	0.483	**0.036**
	65-75	13527	1.04 (1.00-1.08)	**0.042**	
	>75	4744	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Race	White	33083	0.94 (0.89-0.98)	**0.004**	**0.006**
	Black	4385	0.92 (0.87-0.97)	**0.002**	
	Other	2003	-	**-**	
Insurance Type	Not Insured	859	1.02 (0.95-1.10)	0.561	**0.043**
	Private Insurance	22509	0.98 (0.96-1.00)	**0.022**	
	Government Insurance	16103	-	**-**	
Median Income Quartiles 2000	< $30,000	4343	1.01 (0.97-1.04)	0.627	0.440
	$30,000 - $35,999	6255	1.00 (0.97-1.03)	0.998	
	$36,000 - $45,999	10460	0.98 (0.96-1.01)	0.173	
	$46,000 +	18413	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	5746	1.02 (0.99-1.05)	0.169	**0.046**
	20 – 28.9%	8340	0.98 (0.95-1.00)	0.092	
	14 – 19.9%	9024	1.01 (0.99-1.04)	0.373	
	< 14%	16361	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	33555	0.93 (0.86-1.00)	0.061	0.050
	Urban	5209	0.95 (0.88-1.03)	0.247	
	Rural	707	-	-	
Distance	<= 5 miles	11855	0.93 (0.90-0.95)	**<.001**	**<.001**
	5 - 10 miles	9628	0.96 (0.94-0.99)	**0.009**	
	10 - 15 miles	5677	0.94 (0.91-0.97)	**<.001**	
	> 15 miles	12311	-	-	
Charlson-Deyo Score	0	33190	0.99 (0.93-1.06)	0.786	0.726
	1	5221	1.00 (0.93-1.08)	0.943	
	2	1060	-	-	
Pathologic T	T1	27730	1.09 (1.02-1.16)	**0.012**	**0.002**
	T2	10714	1.06 (0.99-1.13)	0.115	
	T3	1027	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	27365	0.91 (0.87-0.96)	**<.001**	**<.001**
	N1	8059	0.88 (0.83-0.93)	**<.001**	
	N2	2287	0.83 (0.78-0.89)	**<.001**	
	NX	1760	-	**-**	
Year of Diagnosis	2010	8860	0.00 (0.00-0.00)	**<.001**	**<.001**
	2011	9635	0.03 (0.03-0.03)	**<.001**	
	2012	10065	0.16 (0.16-0.17)	**<.001**	
	2013	10911	-	**-**	

Table 20: Multivariable Cox Proportional Hazard Ratio for HER2+/HR+ Chemotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	39471	0.5 (0.43-0.56)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	4445	1.03 (0.99-1.08)	0.167	0.165
	Comprehensive Community Cancer Program	18720	1.03 (1.00-1.07)	0.087	
	Academic/Research Program	12048	1.01 (0.97-1.05)	0.627	
	Integrated Network Cancer Program	4258	-	-	
Facility Location	Northeast	8445	0.99 (0.95-1.02)	0.421	0.103
	South	14606	0.98 (0.95-1.02)	0.325	
	Midwest	10141	0.96 (0.93-0.99)	**0.019**	
	West	6279	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Median Income Quartiles 2000	< $30,000	4343	1.05 (1.00-1.10)	**0.031**	0.102
	$30,000 - $35,999	6255	1.01 (0.98-1.05)	0.480	
	$36,000 - $45,999	10460	1.00 (0.97-1.03)	0.849	
	$46,000 +	18413	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	5746	0.98 (0.94-1.03)	0.424	**0.034**
	20 – 28.9%	8340	0.96 (0.93-1.00)	**0.028**	
	14 – 19.9%	9024	1.01 (0.98-1.04)	0.496	
	< 14%	16361	-	-	
Urban/Rural 2003	Metro	33555	0.95 (0.87-1.03)	0.179	0.167
	Urban	5209	0.93 (0.86-1.01)	0.075	
	Rural	707	-	-	
Distance	<= 5 miles	11855	0.96 (0.93-0.98)	**0.002**	**0.002**
	5 - 10 miles	9628	0.95 (0.92-0.98)	**0.001**	
	10 - 15 miles	5677	0.95 (0.92-0.98)	**0.002**	
	> 15 miles	12311	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Charlson-Deyo Score	0	33190	1.00 (0.93-1.07)	0.997	0.094
	1	5221	0.97 (0.90-1.04)	0.358	
	2	1060	-	-	
Pathologic T	T1	27730	1.07 (1.00-1.14)	0.059	0.069
	T2	10714	1.05 (0.98-1.12)	0.191	
	T3	1027	-	-	
Pathologic N	N0	27365	0.99 (0.94-1.04)	0.629	**<.001**
	N1	8059	0.95 (0.90-1.00)	0.052	
	N2	2287	0.92 (0.86-0.98)	**0.010**	
	NX	1760	-	-	
Year of Diagnosis	2010	8860	0.00 (0.00-0.00)	**<.001**	**<.001**
	2011	9635	0.03 (0.03-0.03)	**<.001**	
	2012	10065	0.16 (0.16-0.17)	**<.001**	
	2013	10911	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**

* Number of observations in the original data set = 39471. Number of observations used = 39471.

** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Age at Diagnosis (C), Insurance Type, and race_cat.

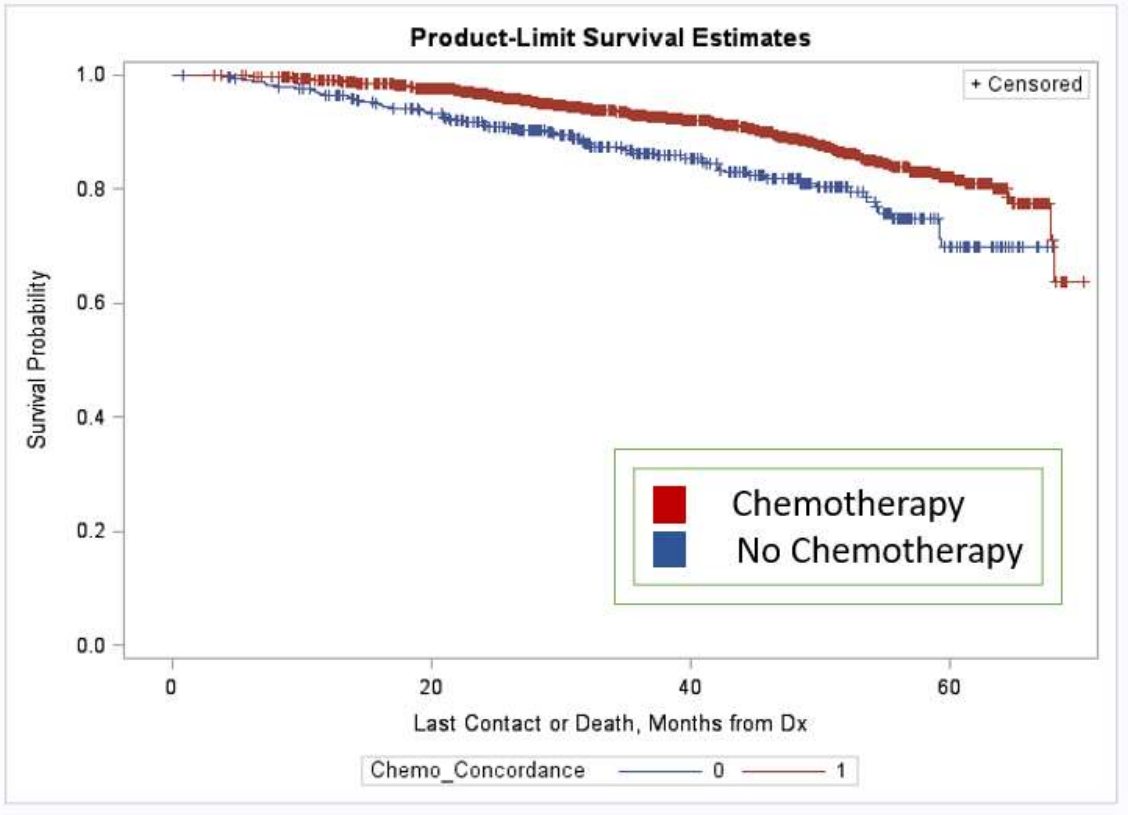


Figure 7: Kaplan Meier Curve for HER2+/HR+ Breast Cancer

Table 21: Descriptive Statistics for All Variables- Triple Negative Chemotherapy

Variable	Level	N (%) = 50064
Chemotherapy Receipt	No	8427 (16.8)
	Yes	41637 (83.2)
Facility Type	Community Cancer Program/Other	5358 (10.7)
	Comprehensive Community Cancer Program	23038 (46.0)
	Academic/Research Program	15692 (31.3)
	Integrated Network Cancer Program	5976 (11.9)
Facility Location	Northeast	9852 (19.7)
	South	19848 (39.6)
	Midwest	13182 (26.3)
	West	7182 (14.3)
Age at Diagnosis (C)	<65	25479 (50.9)
	65-75	17947 (35.8)
	>75	6638 (13.3)
race_cat	White	38020 (75.9)
	Black	10174 (20.3)
	Other	1870 (3.7)
Insurance Type	Not Insured	1141 (2.3)
	Private Insurance	26655 (53.2)
	Government Insurance	22268 (44.5)

Variable	Level	N (%) = 50064
Median Income Quartiles 2000	< $30,000	6453 (12.9)
	$30,000 - $35,999	8429 (16.8)
	$36,000 - $45,999	13718 (27.4)
	$46,000 +	21464 (42.9)
Percent No High School Degree Quartiles 2000	>= 29%	8352 (16.7)
	20 – 28.9%	11398 (22.8)
	14 – 19.9%	11323 (22.6)
	< 14%	18991 (37.9)
Urban/Rural 2003	Metro	42524 (84.9)
	Urban	6687 (13.4)
	Rural	853 (1.7)
Distance	<= 5 miles	15148 (30.3)
	5 - 10 miles	12560 (25.1)
	10 - 15 miles	7072 (14.1)
	> 15 miles	15284 (30.5)
Charlson-Deyo Score	0	40888 (81.7)
	1	7383 (14.7)
	2	1793 (3.6)
Pathologic T	T1	31279 (62.5)
	T2	16826 (33.6)
	T3	1959 (3.9)

Variable	Level	N (%) = 50064
Pathologic N	N0	37071 (74.0)
	N1	8871 (17.7)
	N2	2428 (4.8)
	NX	1694 (3.4)
Year of Diagnosis	2009	1402 (2.8)
	2010	11097 (22.2)
	2011	12427 (24.8)
	2012	12362 (24.7)
	2013	12776 (25.5)

Table 22: Univariate Association with Study Cohort- Triple Negative Chemotherapy

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%)=8427**	**Yes (%) =41637**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	1037 (12.3)	4321 (10.4)	**<.001**
	Comprehensive Community Cancer Program	4198 (49.8)	18840 (45.3)	
	Academic/Research Program	2283 (27.0)	13409 (32.2)	
	Integrated Network Cancer Program	909 (10.8)	5067 (12.2)	
Facility Location	Northeast	1662 (19.7)	8190 (19.7)	**<.001**
	South	3335 (39.6)	16513 (39.7)	
	Midwest	2096 (24.9)	11086 (26.6)	
	West	1334 (15.8)	5848 (14.0)	
Age at Diagnosis (C)	<65	1626 (19.3)	23853 (57.3)	**<.001**
	65-75	2900 (34.4)	15047 (36.1)	
	>75	3901 (46.3)	2737 (6.6)	

Covariate	Level	Receipt of Chemotherapy: No (%)=8427	Receipt of Chemotherapy: Yes (%) =41637	Parametric P-value*
Race	White	6703 (79.5)	31317 (75.2)	**<.001**
	Black	1453 (17.2)	8721 (21.0)	
	Other	271 (3.2)	1599 (3.8)	
Insurance Type	Not Insured	99 (1.2)	1042 (2.5)	**<.001**
	Private Insurance	2219 (26.3)	24436 (58.7)	
	Government Insurance	6109 (72.5)	16159 (38.8)	
Median Income Quartiles 2000	< $30,000	1143 (13.6)	5310 (12.8)	**<.001**
	$30,000 - $35,999	1470 (17.4)	6959 (16.7)	
	$36,000 - $45,999	2365 (28.1)	11353 (27.3)	
	$46,000 +	3449 (40.9)	18015 (43.3)	
Percent No High School Degree Quartiles 2000	>= 29%	1428 (17.0)	6924 (16.6)	0.106
	20 – 28.9%	1862 (22.1)	9536 (22.9)	
	14 – 19.9%	1977 (23.5)	9346 (22.5)	
	< 14%	3160 (37.5)	15831 (38.0)	

		Receipt of Chemotherapy		
Covariate	**Level**	**No (%)=8427**	**Yes (%) =41637**	**Parametric P-value***
Urban/Rural 2003	Metro	7155 (84.9)	35369 (85.0)	0.389
	Urban	1114 (13.2)	5573 (13.4)	
	Rural	158 (1.9)	695 (1.7)	
Distance	<= 5 miles	3013 (35.8)	12135 (29.1)	**<.001**
	5 - 10 miles	2099 (24.9)	10461 (25.1)	
	10 - 15 miles	1069 (12.7)	6003 (14.4)	
	> 15 miles	2246 (26.7)	13038 (31.3)	
Charlson-Deyo Score	0	6262 (74.3)	34626 (83.2)	**<.001**
	1	1584 (18.8)	5799 (13.9)	
	2	581 (6.9)	1212 (2.9)	
Pathologic T	T1	4773 (56.6)	26506 (63.7)	**<.001**
	T2	3215 (38.2)	13611 (32.7)	
	T3	439 (5.2)	1520 (3.7)	

Covariate	Level	Receipt of Chemotherapy		Parametric P-value*
		No (%)=8427	Yes (%) =41637	
Pathologic N	N0	6316 (75.0)	30755 (73.9)	**<.001**
	N1	1044 (12.4)	7827 (18.8)	
	N2	272 (3.2)	2156 (5.2)	
	NX	795 (9.4)	899 (2.2)	
Year of Diagnosis	2009	183 (2.2)	1219 (2.9)	**<.001**
	2010	1957 (23.2)	9140 (22.0)	
	2011	2079 (24.7)	10348 (24.9)	
	2012	2108 (25.0)	10254 (24.6)	
	2013	2100 (24.9)	10676 (25.6)	

* The parametric p-value is calculated by chi-square test. Percentage are calculated within individual category.

Table 23: Multivariable Logistic Regression Model for Triple Negative Chemotherapy

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Facility Type	Community Cancer Program/Other	0.80 (0.71-0.90)	**0.027**	**.0001**
	Comprehensive Community Cancer Program	0.85 (0.77-0.93)	**0.0043**	
	Academic/Research Program	0.92 (0.84-1.01)	0.24	
	Integrated Network Cancer Program	-	-	
Facility Location	Northeast	1.20 (1.10-1.32)	0.07	**<.0001**
	South	1.09 (1.00-1.18)	**0.03**	
	Midwest	1.30 (1.19-1.42)	**<.001**	
	West	-	-	

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Age at Diagnosis (C)	50 and below	15.76 (8.91-27.86)	**<.001**	**<.001**
	51 - 60	7.35 (4.79-11.28)	**<.001**	
	61 - 70	6.41 (4.67-8.79)	**<.001**	
	>70	-	-	
Insurance Type	Not Insured	0.90 (0.72-1.13)	0.27	**<.001**
	Government Insurance	0.65 (0.61-0.70)	**<.001**	
	Private	-		
Charlson-Deyo Score	0	1.76 (1.56-1.99)	**<.001**	**<.001**
	1	1.51 (1.32-1.72)	**0.006**	
	2	-	-	
Pathologic T	T1	1.93 (1.68-2.21)	**0.001**	**0.001**
	T2	1.31 (1.14-1.5)	0.19	
	T3	-	-	

		Receipt of Chemotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Pathologic N	N0	2.68 (2.37-3.03)	**<.001**	**<.001**
	N1	4.84 (4.21-5.57)	**<.001**	
	N2	6.30 (5.22-7.59)	**<.001**	
	NX	-	-	
Year of Diagnosis	2010	0.87 (0.80-0.94)	**0.0002**	**0.0043**
	2011	0.95 (0.89-1.03)	0.49	
	2012	0.96 (0.89-1.03)	0.60	
	2013	-	-	

Table 24: Univariate Association with Overall Survival – Triple Negative Chemotherapy

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	50064	0.37 (0.34-0.39)	**0.002**	**0.002**
Facility Type	Community Cancer Program/Other	5358	1.00 (0.96-1.04)	0.812	0.253
	Comprehensive Community Cancer Program	23038	1.00 (0.97-1.03)	0.896	
	Academic/Research Program	15692	1.02 (0.99-1.05)	0.198	
	Integrated Network Cancer Program	5976	-	-	
Facility Location	Northeast	9852	0.99 (0.96-1.02)	0.627	**<.001**
	South	19848	0.95 (0.93-0.98)	**0.001**	
	Midwest	13182	0.99 (0.96-1.02)	0.528	
	West	7182	-	-	
Age at Diagnosis (C)	<65	25479	0.96 (0.93-0.99)	**0.011**	**<.001**
	65-75	17947	1.00 (0.97-1.03)	0.934	
	>75	6638	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Race	White	38020	0.93 (0.89-0.98)	**0.005**	**0.019**
	Black	10174	0.94 (0.89-0.99)	**0.013**	
	Other	1870	-	**-**	
Insurance Type	Not Insured	1141	0.99 (0.93-1.06)	0.829	**<.001**
	Private Insurance	26655	0.95 (0.94-0.97)	**<.001**	
	Government Insurance	22268	-	**-**	
Median Income Quartiles 2000	< $30,000	6453	0.97 (0.94-1.00)	0.056	0.105
	$30,000 - $35,999	8429	0.97 (0.95-1.00)	0.065	
	$36,000 - $45,999	13718	1.00 (0.97-1.02)	0.779	
	$46,000 +	21464	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	8352	0.97 (0.94-0.99)	**0.018**	**0.039**
	20 – 28.9%	11398	0.99 (0.96-1.01)	0.381	
	14 – 19.9%	11323	1.01 (0.98-1.03)	0.491	
	< 14%	18991	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	42524	1.02 (0.95-1.09)	0.631	0.262
	Urban	6687	1.00 (0.92-1.07)	0.906	
	Rural	853	-	-	
Distance	<= 5 miles	15148	0.96 (0.94-0.99)	**0.002**	**0.024**
	5 - 10 miles	12560	0.98 (0.96-1.01)	0.160	
	10 - 15 miles	7072	0.98 (0.95-1.01)	0.211	
	> 15 miles	15284	-	-	
Charlson-Deyo Score	0	40888	0.93 (0.88-0.98)	**0.007**	**<.001**
	1	7383	0.98 (0.92-1.04)	0.414	
	2	1793	-	-	
Pathologic T	T1	31279	1.12 (1.06-1.19)	**<.001**	**<.001**
	T2	16826	1.07 (1.01-1.13)	**0.030**	
	T3	1959	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	37071	0.97 (0.92-1.03)	0.279	**<.001**
	N1	8871	0.90 (0.84-0.95)	**<.001**	
	N2	2428	0.85 (0.79-0.92)	**<.001**	
	NX	1694	-	**-**	
Year of Diagnosis	2009	1402	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	11097	0.00 (0.00-0.01)	**<.001**	
	2011	12427	0.03 (0.03-0.03)	**<.001**	
	2012	12362	0.17 (0.16-0.17)	**<.001**	
	2013	12776	-	**-**	

Table 25: Multivariate Cox Proportional Hazard Model for Overall Survival- Triple Negative Chemotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Chemotherapy Receipt	Yes	50064	0.50 (0.45-0.53)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	5358	1.06 (1.01-1.10)	**0.008**	0.061
	Comprehensive Community Cancer Program	23038	1.02 (0.99-1.05)	0.212	
	Academic/Research Program	15692	1.02 (0.99-1.06)	0.163	
	Integrated Network Cancer Program	5976	-	-	
Race	White	38020	0.94 (0.89-0.98)	**0.008**	**0.007**
	Black	10174	0.92 (0.87-0.97)	**0.002**	
	Other	1870	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Distance	<= 5 miles	15148	0.96 (0.93-0.98)	**<.001**	**<.001**
	5 - 10 miles	12560	0.98 (0.96-1.01)	0.162	
	10 - 15 miles	7072	0.95 (0.92-0.97)	**<.001**	
	> 15 miles	15284	-	-	
Charlson-Deyo Score	0	40888	1.07 (1.01-1.13)	**0.015**	0.050
	1	7383	1.07 (1.01-1.14)	**0.023**	
	2	1793	-	-	
Pathologic N	N0	37071	0.95 (0.90-1.01)	0.099	**<.001**
	N1	8871	0.90 (0.85-0.96)	**<.001**	
	N2	2428	0.92 (0.85-0.99)	**0.023**	
	NX	1694	-	-	
Year of Diagnosis	2009	1402	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	11097	0.00 (0.00-0.00)	**<.001**	
	2011	12427	0.03 (0.03-0.03)	**<.001**	
	2012	12362	0.17 (0.16-0.17)	**<.001**	
	2013	12776	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**

* Number of observations in the original data set = 50064. Number of observations used = 50064.

** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Age at Diagnosis (C), Facility Location, Median Income Quartiles 2000, Percent No High School Degree Quartiles 2000, Pathologic T, Urban/Rural 2003, and Insurance Type.

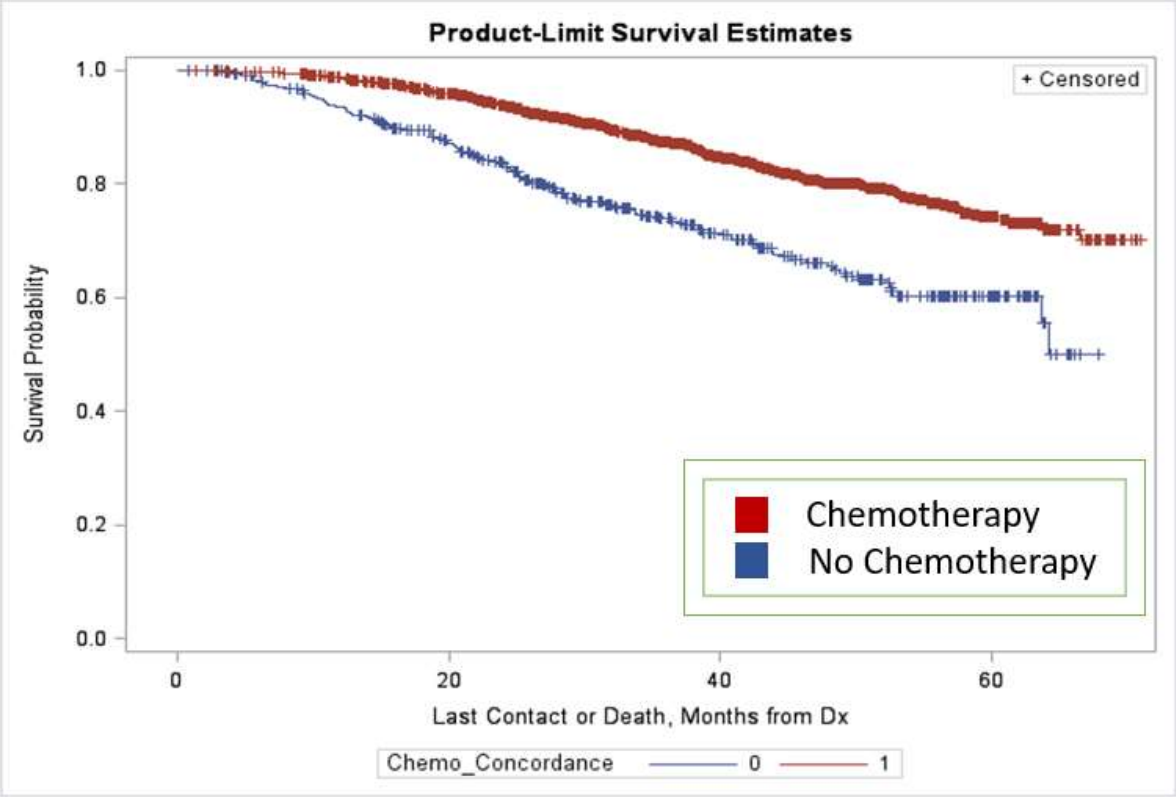


Figure 8: Kaplan Meier Curve for Triple Negative Chemotherapy

Immunotherapy

Human epidermal growth factor -2 (HER-2) is a tyrosine-protein kinase that is highly involved in growth and differentiation. HER-2 overexpression in breast cancer is associated with an aggressive clinical phenotype that results in high-grade disease, early metastasis, and decreased overall survival [86]. This amplification occurs in 20-25% of human breast cancers [87]. The recombinant HER-2 monoclonal antibody trastuzumab was first introduced to the market in 1996. Since then, several landmark trials have demonstrated the efficacy of trastuzumab in reducing disease recurrence by as much as 50% and improving rate of survival by as much as 30% in cancers that are HER-2 positive [88, 89]. The Breast Cancer International Research Group 006 (BCIRG-006) trial demonstrated that the addition of one year of adjuvant nonanthracycline trastuzumab regimen significantly improved disease-free and overall survival in HER-2-positive patients with fewer acute toxic effects.

The effectiveness of trastuzumab immunotherapy has led to its inclusion in many evidence-based treatment guidelines. The American Society of Clinical Oncology (ASCO) recommends HER-2-targeted therapy-based combinations for first-line treatment in patients with advanced HER2-positive breast cancer, with the exception of a specific subset of patients with estrogen receptor (ER) positive or progesterone receptor (PR) positive HER2-positive disease that benefits from the improved toxicity profiles of an endocrine-only regimen [90]. For patients with early-stage breast cancer, defined as malignancy that has not spread beyond the breast or axillary lymph nodes (stage I, stage IIA, stage IIB, and stage IIIA), ASCO recommends the use of immunotherapy for all patients with HER-2-positive, node-positive breast cancer and for patients with HER-2-positive, node negative breast cancer greater than 1 cm [38]. This guideline for early-stage breast cancer is also endorsed by the National Comprehensive Cancer Network (NCCN), which also recommends the consideration of trastuzumab therapy for patients with tumors 0.5 - 0.9 cm as well [67].

Immunotherapy Receipt from 2010-2013

From 2010-2013, 54,340 patients were eligible for immunotherapy; there were 17,396 patients with HER2+/HR2- disease and 39,644 patients with HER2+/HR2+ disease. Selection criteria are listed in **Figure 8**. Median age of the entire cohort was 68 years and median follow-up time was 35.8 months. Receipt of immunotherapy rose from 24.34% to 69.30%, with an overall compliance of 38.24%. Baseline characteristics and unadjusted outcomes between eligible patient who received immunotherapy and who did not receive immunotherapy are reported in (**Table 26**).

Univariate Factors Associated with Immunotherapy Underuse in HER2+/HR- Cancers

Several variables were associated with immunotherapy compliance on UVA (**Table 27**). Academic/research programs had the highest compliance rates (52.5%) and community cancer programs had the lowest compliance rate (47.7%) (P<.001). Geographically, patients in the Northeast had the highest rates of treatment (52.05%) with the lowest rates seen in the West (48.2%) (P<.001). Other factors associated with higher compliance included patients 65-75 years of age, white race, with private insurance, living in a zip code with greater than 83% high school graduation, earning greater than $46,000, living in a rural setting, having T0/N1 staging, and being diagnosed in 2013.

Univariate Factors Associated with Immunotherapy Underuse in HER2+/HR+ Cancers

Baseline characteristics are listed in **Table 28**. Several variables were associated with immunotherapy compliance on UVA (**Table 29**). Again, academic/research programs had the highest compliance rates (54.3%) and community cancer programs had the lowest compliance rate (46.6%) (P<.001). Geographically, patients in the Northeast and Midwest had the highest rates of treatment while the West and South had lower rates (P<.001). Other factors associated with high compliance included patients 65-75 years of age, white race, having private insurance, living in a zip code with greater than 83% high school graduation, earning greater than $46,000, living in an urban setting, having T0/N1 staging, and being diagnosed in 2013.

Multivariate Factors Associated with Immunotherapy Underuse in HER2+ Cancers

On MVA, factors associated with immunotherapy compliance included treatment at an academic/research program versus integrated network cancer program (OR 1.185 95% CI 1.047-1.342), treatment in the Northeast and Midwest (versus West) (OR 1.196 95% CI 1.06-1.35 and OR 1.15 95% CI 1.03-1.30, respectively), being white (versus black), being 75 years or younger (versus 75 years and older), having private insurance (versus government insurance), living in an area code with greater than 83% high school graduation rate with between 71.1%-80% high school graduation rate, being treated at a facility 15 miles away or less (versus more), having pathologic T1 tumor staging versus T3 tumor staging, and having unknown pathologic NX tumor staging (versus N1) (**Table 30**).

Effectiveness of Immunotherapy Receipt when Recommended by Evidence-Based Guidelines

Univariate survival analyses were sub-divided into HER2+/HR- patients and HER2+/HR+ patients. There is increased mortality with non-guideline concordant care compared to guideline concordant care for both HER2+/HR- breast cancer (unadjusted HR 2.04 CI 1.76 – 2.36 p = <.0001). In the multivariable Cox proportional hazards model adjusted for age, race, hormone receptor status, facility type, facility location, income level, percent of population with high school degrees, urbanicity, Charlson-Deyo comorbidity index, AJCC pathologic T staging, AJCC pathology N staging, year of diagnosis, and distance, non-guideline concordant immunotherapy care resulted in an 81% increase in mortality (adjusted HR 1.82 CI 1.55 – 2.13; p = <.0001) **(Table 32**) This was also true for the HER2+/HR+ population (unadjusted HR 1.82 CI 1.63 – 2.03; adjusted HR 1.46 CI 1.29 – 1.64 p = <.0001) (**Table 33**). We explored the heterogeneity effect of immunotherapy treatment with several clinical factors and found it was significant (p = < .0001) for hormone status, facility type, age, insurance, Charlson-Deyo comorbidity index, AJCC T and N staging, and year of diagnosis (**Table 34 and 35**). Overall three-year survival for HER2+/HR- patient was 92.1% in compliant patients and 88.3% for noncompliant patients. Overall 3-year

survival for HER+/HR+ patients was 94.3% and 92.1%, respectively. **Figure 9** demonstrates the Kaplan-

Meier curves for overall survival for eligible patients who received immunotherapy versus those who did

not for HER2+/HR- patients (a) and HER2+/HR+ patients (b).

Immunotherapy Figures

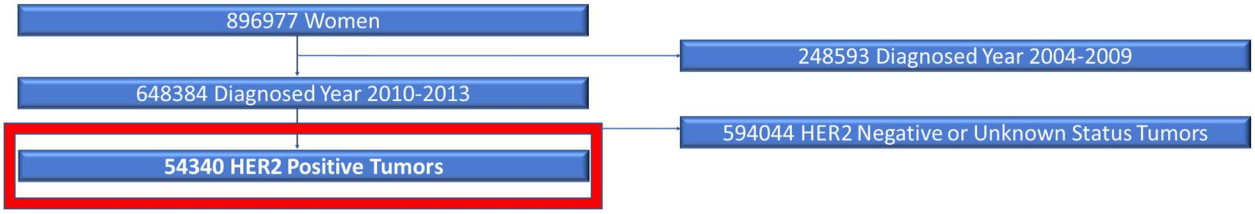


Figure 8: Selection Criteria for Immunotherapy

Table 26: Descriptive Statistics for HER2+/HR- Immunotherapy

Variable	Level	N (%) = 17396
Immunotherapy Receipt	No	10397 (59.8)
	Yes	6999 (40.2)
Facility Type	Community Cancer Program/Other	1820 (10.5)
	Comprehensive Community Cancer Program	8123 (46.7)
	Academic/Research Program	5485 (31.5)
	Integrated Network Cancer Program	1968 (11.3)
Facility Location	Northeast	3646 (21.0)
	South	6578 (37.8)
	Midwest	4502 (25.9)
	West	2670 (15.3)

Variable	Level	N (%) = 17396
Age at Diagnosis (C)	<65	9398 (54.0)
	65-75	6053 (34.8)
	>75	1945 (11.2)
race_cat	White	13918 (80.0)
	Black	2396 (13.8)
	Other	1082 (6.2)
Insurance Type	Not Insured	409 (2.4)
	Private Insurance	9879 (56.8)
	Government Insurance	7108 (40.9)
Median Income Quartiles 2000	< $30,000	1980 (11.4)
	$30,000 - $35,999	2820 (16.2)
	$36,000 - $45,999	4683 (26.9)
	$46,000 +	7913 (45.5)
Percent No High School Degree Quartiles 2000	>= 29%	2740 (15.8)
	20 – 28.9%	3673 (21.1)
	14 – 19.9%	3978 (22.9)
	< 14%	7005 (40.3)
Urban/Rural 2003	Metro	14857 (85.4)
	Urban	2243 (12.9)
	Rural	296 (1.7)
Distance	<= 4 miles	4066 (23.4)
	4 - 8.4 miles	4151 (23.9)
	8.4 - 17.6 miles	4518 (26.0)
	> 17.6 miles	4661 (26.8)

Variable	Level	N (%) = 17396
Charlson-Deyo Score	0	14639 (84.2)
	1	2279 (13.1)
	2	478 (2.7)
Pathologic T	T1	12282 (70.6)
	T2	4546 (26.1)
	T3	568 (3.3)
Pathologic N	N0	12215 (70.2)
	N1	3314 (19.1)
	N2	1088 (6.3)
	NX	779 (4.5)
Year of Diagnosis	2009	487 (2.8)
	2010	3910 (22.5)
	2011	4165 (23.9)
	2012	4271 (24.6)
	2013	4563 (26.2)

Table 27: Univariate Association with Study Cohort- HER2+/HR- Immunotherapy

		Receipt of Immunotherapy		
Covariate	**Level**	**No (%)=10397**	**Yes (%)=6999**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	1146 (11.0)	674 (9.6)	**<.001**
	Comprehensive Community Cancer Program	4989 (48.0)	3134 (44.8)	
	Academic/Research Program	3053 (29.4)	2432 (34.8)	
	Integrated Network Cancer Program	1209 (11.6)	759 (10.8)	
Facility Location	Northeast	2035 (19.6)	1611 (23.0)	**<.001**
	South	4096 (39.4)	2482 (35.5)	
	Midwest	2641 (25.4)	1861 (26.6)	
	West	1625 (15.6)	1045 (14.9)	
Age at Diagnosis (C)	<65	5594 (53.8)	3804 (54.4)	**<.001**
	65-75	3497 (33.6)	2556 (36.5)	
	>75	1306 (12.6)	639 (9.1)	

Covariate	Level	Receipt of Immunotherapy: No (%)=10397	Receipt of Immunotherapy: Yes (%)=6999	Parametric P-value*
Race	White	8268 (79.5)	5650 (80.7)	**<.001**
	Black	1510 (14.5)	886 (12.7)	
	Other	619 (6.0)	463 (6.6)	
Insurance Type	Not Insured	248 (2.4)	161 (2.3)	**<.001**
	Private Insurance	5744 (55.2)	4135 (59.1)	
	Government Insurance	4405 (42.4)	2703 (38.6)	
Median Income Quartiles 2000	< $30,000	1260 (12.1)	720 (10.3)	**<.001**
	$30,000 - $35,999	1761 (16.9)	1059 (15.1)	
	$36,000 - $45,999	2835 (27.3)	1848 (26.4)	
	$46,000 +	4541 (43.7)	3372 (48.2)	
Percent No High School Degree Quartiles 2000	>= 29%	1711 (16.5)	1029 (14.7)	**<.001**
	20 – 28.9%	2299 (22.1)	1374 (19.6)	
	14 – 19.9%	2381 (22.9)	1597 (22.8)	
	< 14%	4006 (38.5)	2999 (42.9)	

Covariate	Level	Receipt of Immunotherapy: No (%)=10397	Receipt of Immunotherapy: Yes (%)=6999	Parametric P-value*
Urban/Rural 2003	Metro	8793 (84.6)	6064 (86.6)	**<.001**
	Urban	1414 (13.6)	829 (11.8)	
	Rural	190 (1.8)	106 (1.5)	
Distance	<= 4 miles	2445 (23.5)	1621 (23.2)	0.923
	4 - 8.4 miles	2472 (23.8)	1679 (24.0)	
	8.4 - 17.6 miles	2688 (25.9)	1830 (26.2)	
	> 17.6 miles	2792 (26.9)	1869 (26.7)	
Charlson-Deyo Score	0	8693 (83.6)	5946 (85.0)	**0.014**
	1	1392 (13.4)	887 (12.7)	
	2	312 (3.0)	166 (2.4)	
Pathologic T	T1	6206 (59.7)	6076 (86.8)	**<.001**
	T2	3722 (35.8)	824 (11.8)	
	T3	469 (4.5)	99 (1.4)	

Covariate	Level	Receipt of Immunotherapy: No (%)=10397	Receipt of Immunotherapy: Yes (%)=6999	Parametric P-value*
Pathologic N	N0	6647 (63.4)	5568 (79.6)	**<.001**
	N1	2469 (23.8)	845 (12.1)	
	N2	895 (8.6)	193 (2.7)	
	NX	386 (3.7)	393 (5.6)	
Year of Diagnosis	2009	370 (3.6)	117 (1.7)	**<.001**
	2010	2843 (27.3)	1067 (15.3)	
	2011	2994 (28.8)	1171 (16.7)	
	2012	2904 (27.9)	1367 (19.5)	
	2013	1286 (12.4)	3277 (46.8)	

* The parametric p-value is calculated by chi-square test. All percentages are calculated within individual category

Table 28: Baseline Characteristics for Study Cohort: HER2+/HR+ Breast Cancer

Variable	Level	N (%) = 39644
Immunotherapy Receipt	No	24816 (62.6)
	Yes	14828 (37.4)
Facility Type	Community Cancer Program/Other	4472 (11.3)
	Comprehensive Community Cancer Program	18795 (47.4)
	Academic/Research Program	12082 (30.5)
	Integrated Network Cancer Program	4295 (10.8)
Facility Location	Northeast	8348 (21.1)
	South	14803 (37.3)
	Midwest	10161 (25.6)
	West	6332 (16.0)
Age at Diagnosis (C)	<65	21340 (53.8)
	65-75	13535 (34.1)
	>75	4769 (12.0)
Race	White	33219 (83.8)
	Black	4410 (11.1)
	Other	2015 (5.1)
Insurance Type	Not Insured	854 (2.2)
	Private Insurance	22640 (57.1)
	Government Insurance	16150 (40.7)

Variable	Level	N (%) = 39644
Median Income Quartiles 2000	< $30,000	4392 (11.1)
	$30,000 - $35,999	6289 (15.9)
	$36,000 - $45,999	10482 (26.4)
	$46,000 +	18481 (46.6)
Percent No High School Degree Quartiles 2000	>= 29%	5785 (14.6)
	20 – 28.9%	8395 (21.2)
	14 – 19.9%	9061 (22.9)
	< 14%	16403 (41.4)
Urban/Rural 2003	Metro	33677 (84.9)
	Urban	5244 (13.2)
	Rural	723 (1.8)
Distance	<= 5 miles	11870 (29.9)
	5 - 10 miles	9678 (24.4)
	10 - 15 miles	5674 (14.3)
	> 15 miles	12422 (31.3)
Charlson-Deyo Score	0	33362 (84.2)
	1	5224 (13.2)
	2	1058 (2.7)
Pathologic T	T1	27623 (69.7)
	T2	10967 (27.7)
	T3	1054 (2.7)

Variable	Level	N (%) = 39644
Pathologic N	N0	27446 (69.2)
	N1	8219 (20.7)
	N2	2366 (6.0)
	NX	1613 (4.1)
Year of Diagnosis	2009	931 (2.3)
	2010	8635 (21.8)
	2011	9450 (23.8)
	2012	9873 (24.9)
	2013	10755 (27.1)

Table 29: Univariate Association with Study Cohort Immunotherapy- HER2+/HR+

		Receipt of Immunotherapy		
Covariate	**Level**	**No (%) =24816**	**Yes (%) =14828**	**Parametric P-value***
Facility Type	Community Cancer Program/Other	2894 (11.7)	1578 (10.6)	**<.001**
	Comprehensive Community Cancer Program	11953 (48.2)	6842 (46.1)	
	Academic/Research Program	7272 (29.3)	4810 (32.4)	
	Integrated Network Cancer Program	2697 (10.9)	1598 (10.8)	
Facility Location	Northeast	5063 (20.4)	3285 (22.2)	**<.001**
	South	9413 (37.9)	5390 (36.4)	
	Midwest	6271 (25.3)	3890 (26.2)	
	West	4069 (16.4)	2263 (15.3)	
Age at Diagnosis (C)	<65	13167 (53.1)	8173 (55.12)	**<.001**
	65-75	8276 (33.4)	5259 (35.5)	
	>75	3373 (13.6)	1396 (9.4)	

		Receipt of Immunotherapy		
Covariate	**Level**	**No (%) =24816**	**Yes (%) =14828**	**Parametric P-value***
Race	White	20683 (83.4)	12536 (84.5)	**<.001**
	Black	2877 (11.6)	1533 (10.3)	
	Other	1256 (5.1)	759 (5.1)	
Insurance Type	Not Insured	544 (2.19)	310 (2.09)	**<.001**
	Private Insurance	13768 (55.48)	8872 (59.83)	
	Government Insurance	10504 (42.33)	5646 (38.08)	
Median Income Quartiles 2000	< $30,000	2844 (11.5)	1548 (10.4)	**<.001**
	$30,000 - $35,999	4017 (16.2)	2272 (15.3)	
	$36,000 - $45,999	6586 (26.5)	3896 (26.3)	
	$46,000 +	11369 (45.8)	7112 (48.0)	
Percent No High School Degree Quartiles 2000	>= 29%	3707 (14.9)	2078 (14.01)	**<.001**
	20 – 28.9%	5493 (22.1)	2902 (19.6)	
	14 – 19.9%	5540 (22.3)	3521 (23.8)	
	< 14%	10076 (40.6)	6327 (42.7)	

		Receipt of Immunotherapy		
Covariate	**Level**	**No (%) =24816**	**Yes (%) =14828**	**Parametric P-value***
Urban/Rural 2003	Metro	21050 (84.8)	12627 (85.2)	0.403
	Urban	3322 (13.4)	1922 (13.0)	
	Rural	444 (1.8)	279 (1.89)	
Distance	<= 5 miles	7487 (30.2)	4383 (29.6)	0.249
	5 - 10 miles	6037 (24.3)	3641 (24.6)	
	10 - 15 miles	3588 (14.5)	2086 (14.1)	
	> 15 miles	7704 (31.0)	4718 (31.8)	
Charlson-Deyo Score	0	20753 (83.6)	12609 (85.0)	**<.001**
	1	3356 (13.5)	1868 (12.6)	
	2	707 (2.9)	351 (2.4)	
Pathologic T	T1	15176 (61.2)	12447 (83.9)	**<.001**
	T2	8788 (35.4)	2179 (14.7)	
	T3	852 (3.4)	202 (1.4)	

Covariate	Level	Receipt of Immunotherapy: No (%) =24816	Receipt of Immunotherapy: Yes (%) =14828	Parametric P-value*
Pathologic N	N0	15867 (63.9)	11579 (78.0)	**<.001**
	N1	6150 (24.8)	2069 (14.0)	
	N2	1883 (7.6)	483 (3.3)	
	NX	916 (3.7)	697 (4.7)	
Year of Diagnosis	2009	739 (3.0)	192 (1.3)	**<.001**
	2010	6586 (26.5)	2049 (13.8)	
	2011	7115 (28.7)	2335 (15.8)	
	2012	7068 (28.5)	2805 (18.9)	
	2013	3308 (13.3)	7447 (50.2)	

* The parametric p-value is calculated by chi-square test. Percentages are calculated within individual categories.

Table 30: Multivariate Logistic Association with Study Cohort: All HER+ Breast Cancer

		Receipt of Immunotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Percent No High School Degree Quartiles 2000	>= 29%	0.61 (0.57-0.65)	**<.001**	**<.001**
	20%-29.0%	0.80 (0.76-0.85)	**<.001**	
	14%–19.9%	0.91 (0.87-0.96)	**0.002**	
	< 14%			
Facility Type	Community Cancer Program/Other	0.95 (0.86-1.05)	0.0694	**0.007**
	Comprehensive Community Cancer Program	0.99 (0.92-1.07)	0.5098	
	Academic/Research Program	1.08 (0.99-1.17)	**0.0012**	
	Integrated Network Cancer Program	-	-	
Facility Location	Northeast	1.14 (1.06-1.24)	**0.0147**	**0.004**
	South	1.07 (0.99-1.15)	.5302	
	Midwest	1.12 (1.04-1.21)	0.08	
	West	-	-	
Age at Diagnosis (C)	< 65	1.44 (1.32-1.58)	**<.001**	**<.0001**
	65-75	1.43 (1.32-1.56)	**<.001**	
	>75	-	-	

		Receipt of Immunotherapy		
Covariate	**Level**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Insurance Type	Not Insured	0.94 (0.80-1.11)	0.89	**.0065**
	Government Insurance	0.91 (0.86-0.97)	0.18	
	Private Insurance	-	-	
Pathologic T	T1	3.16 (2.65-3.78)	**<.001**	**<.0001**
	T2	0.91 (0.76-1.09)	**<.001**	
	T3	-	-	
Pathologic N	N0	0.96 (0.85-1.07)	**<.001**	**<.0001**
	N1	0.51 (0.45-0.58)	**<.001**	
	N2	0.50 (0.42-0.58)	**<.001**	
	NX	-	-	
Distance	less than 5 miles	1.03 (0.95-1.10)	0.77	**0.007**
	5 to 10 miles	0.98 (0.91-1.05)	0.022	
	10 to 15 miles	0.94 (0.88-1.01)	0.07	
	greater than 15 miles	-	-	

* Number of observations in the original data set = 54340. Number of observations used = 54340.
** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Charlson-Deyo Score, Median Income Quartiles 2000, Percent No High School Degree Quartiles 2000, Urban/Rural 2003, Year of Diagnosis, and Insurance Type.

Table 31: Univariate Association with Overall Survival: HER2+/HR- Immunotherapy

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Immunotherapy Receipt	Yes	39644	0.49 (0.41-0.56)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	4472	0.96 (0.92-1.00)	0.080	**0.002**
	Comprehensive Community Cancer Program	18795	0.97 (0.94-1.01)	0.105	
	Academic/Research Program	12082	1.01 (0.98-1.05)	0.484	
	Integrated Network Cancer Program	4295	-	**-**	
Facility Location	Northeast	8348	0.98 (0.95-1.01)	0.271	0.155
	South	14803	0.97 (0.94-1.00)	**0.024**	
	Midwest	10161	0.98 (0.95-1.01)	0.171	
	West	6332	-	**-**	
Age at Diagnosis (C)	<65	21340	1.00 (0.96-1.03)	0.899	**0.011**
	65-75	13535	1.03 (0.99-1.07)	0.095	
	>75	4769	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
race_cat	White	33219	0.94 (0.90-0.98)	**0.008**	**0.004**
	Black	4410	0.91 (0.86-0.96)	**<.001**	
	Other	2015	-	**-**	
Insurance Type	Not Insured	854	1.02 (0.95-1.09)	0.611	**0.015**
	Private Insurance	22640	0.97 (0.95-0.99)	**0.007**	
	Government Insurance	16150	-	**-**	
Median Income Quartiles 2000	< $30,000	4392	0.98 (0.95-1.02)	0.303	0.775
	$30,000 - $35,999	6289	1.00 (0.97-1.03)	0.872	
	$36,000 - $45,999	10482	0.99 (0.97-1.02)	0.657	
	$46,000 +	18481	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	5785	1.02 (0.99-1.05)	0.206	**0.011**
	20 – 28.9%	8395	0.97 (0.94-1.00)	**0.021**	
	14 – 19.9%	9061	1.01 (0.98-1.04)	0.406	
	< 14%	16403	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	33677	0.98 (0.91-1.05)	0.546	0.542
	Urban	5244	0.99 (0.91-1.07)	0.830	
	Rural	723	-	-	
Distance	<= 5 miles	11870	0.94 (0.91-0.96)	**<.001**	**<.001**
	5 - 10 miles	9678	0.97 (0.94-1.00)	**0.027**	
	10 - 15 miles	5674	0.96 (0.93-0.99)	**0.006**	
	> 15 miles	12422	-	-	
Charlson-Deyo Score	0	33362	0.98 (0.92-1.05)	0.573	0.161
	1	5224	1.01 (0.94-1.09)	0.795	
	2	1058	-	-	
Pathologic T	T1	27623	1.10 (1.03-1.17)	**0.005**	**<.001**
	T2	10967	1.05 (0.98-1.12)	0.162	
	T3	1054	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	27446	0.90 (0.85-0.95)	**<.001**	**<.001**
	N1	8219	0.86 (0.81-0.91)	**<.001**	
	N2	2366	0.80 (0.75-0.85)	**<.001**	
	NX	1613	-	**-**	
Year of Diagnosis	2009	931	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	8635	0.00 (0.00-0.00)	**<.001**	
	2011	9450	0.03 (0.03-0.03)	**<.001**	
	2012	9873	0.16 (0.16-0.17)	**<.001**	
	2013	10755	-	**-**	

Table 32: Univariate Associate with Overall Survival: HER+/HR+ Immunotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Immunotherapy Receipt	Yes	39644	0.56 (0.5-0.625)	**<.001**	**<.001**
Facility Type	Community Cancer Program/Other	4472	0.96 (0.92-1.00)	0.080	**0.002**
	Comprehensive Community Cancer Program	18795	0.97 (0.94-1.01)	0.105	
	Academic/Research Program	12082	1.01 (0.98-1.05)	0.484	
	Integrated Network Cancer Program	4295	-	-	
Facility Location	Northeast	8348	0.98 (0.95-1.01)	0.271	0.155
	South	14803	0.97 (0.94-1.00)	**0.024**	
	Midwest	10161	0.98 (0.95-1.01)	0.171	
	West	6332	-	-	
Age at Diagnosis (C)	<65	21340	1.00 (0.96-1.03)	0.899	**0.011**
	65-75	13535	1.03 (0.99-1.07)	0.095	
	>75	4769	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
race_cat	White	33219	0.94 (0.90-0.98)	**0.008**	**0.004**
	Black	4410	0.91 (0.86-0.96)	**<.001**	
	Other	2015	-	**-**	
Insurance Type	Not Insured	854	1.02 (0.95-1.09)	0.611	**0.015**
	Private Insurance	22640	0.97 (0.95-0.99)	**0.007**	
	Government Insurance	16150	-	**-**	
Median Income Quartiles 2000	< $30,000	4392	0.98 (0.95-1.02)	0.303	0.775
	$30,000 - $35,999	6289	1.00 (0.97-1.03)	0.872	
	$36,000 - $45,999	10482	0.99 (0.97-1.02)	0.657	
	$46,000 +	18481	-	**-**	
Percent No High School Degree Quartiles 2000	>= 29%	5785	1.02 (0.99-1.05)	0.206	**0.011**
	20 – 28.9%	8395	0.97 (0.94-1.00)	**0.021**	
	14 – 19.9%	9061	1.01 (0.98-1.04)	0.406	
	< 14%	16403	-	**-**	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Urban/Rural 2003	Metro	33677	0.98 (0.91-1.05)	0.546	0.542
	Urban	5244	0.99 (0.91-1.07)	0.830	
	Rural	723	-	-	
Distance	<= 5 miles	11870	0.94 (0.91-0.96)	**<.001**	**<.001**
	5 - 10 miles	9678	0.97 (0.94-1.00)	**0.027**	
	10 - 15 miles	5674	0.96 (0.93-0.99)	**0.006**	
	> 15 miles	12422	-	-	
Charlson-Deyo Score	0	33362	0.98 (0.92-1.05)	0.573	0.161
	1	5224	1.01 (0.94-1.09)	0.795	
	2	1058	-	-	
Pathologic T	T1	27623	1.10 (1.03-1.17)	**0.005**	**<.001**
	T2	10967	1.05 (0.98-1.12)	0.162	
	T3	1054	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	27446	0.90 (0.85-0.95)	**<.001**	**<.001**
	N1	8219	0.86 (0.81-0.91)	**<.001**	
	N2	2366	0.80 (0.75-0.85)	**<.001**	
	NX	1613	-	**-**	
Year of Diagnosis	2009	931	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	8635	0.00 (0.00-0.00)	**<.001**	
	2011	9450	0.03 (0.03-0.03)	**<.001**	
	2012	9873	0.16 (0.16-0.17)	**<.001**	
	2013	10755	-	**-**	

Table 33: Multivariable Cox Proportional Hazard HER2+/HR- Immunotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Immunotherapy Receipt	Yes	17396	0.67 (0.55-0.77)	0.166	0.166
Facility Location	Northeast	3646	1.05 (0.99-1.10)	0.081	0.061
	South	6578	1.05 (1.00-1.10)	**0.047**	
	Midwest	4502	1.01 (0.96-1.06)	0.800	
	West	2670	-	-	
Race	White	13918	1.00 (0.93-1.06)	0.906	**0.018**
	Black	2396	0.93 (0.86-1.01)	0.071	
	Other	1082	-	-	
Insurance Type	Not Insured	409	1.08 (0.98-1.20)	0.124	0.105
	Private Insurance	9879	0.98 (0.95-1.01)	0.248	
	Government Insurance	7108	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Pathologic N	N0	12215	0.95 (0.88-1.02)	0.165	**0.006**
	N1	3314	0.91 (0.84-0.99)	**0.025**	
	N2	1088	0.86 (0.78-0.95)	**0.004**	
	NX	779	-	-	
Year of Diagnosis	2009	487	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	3910	0.00 (0.00-0.01)	**<.001**	
	2011	4165	0.03 (0.03-0.03)	**<.001**	
	2012	4271	0.18 (0.17-0.19)	**<.001**	
	2013	4563	-	-	

* Number of observations in the original data set = 17396. Number of observations used = 17396.

** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Age at Diagnosis (C), Charlson-Deyo Score, Distance, Facility Type, Median Income Quartiles 2000, Percent No High School Degree Quartiles 2000, Pathologic T, and Urban/Rural 2003.

Table 34: Multivariable Cox Proportional Hazard HER2+/HR+ Immunotherapy

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Immunotherapy Receipt	Yes	39644	0.71 (0.625-0.76)	**0.023**	**0.023**
Facility Type	Community Cancer Program/Other	4472	1.03 (0.99-1.08)	0.140	0.164
	Comprehensive Community Cancer Program	18795	1.03 (1.00-1.07)	0.058	
	Academic/Research Program	12082	1.01 (0.98-1.05)	0.447	
	Integrated Network Cancer Program	4295	-	-	
Facility Location	Northeast	8348	0.98 (0.95-1.02)	0.296	**0.017**
	South	14803	0.98 (0.95-1.01)	0.203	
	Midwest	10161	0.95 (0.92-0.98)	**0.003**	
	West	6332	-	-	

			Last Contact or Death, Months from Dx		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Age at Diagnosis (C)	<65	21340	0.96 (0.92-0.99)	**0.011**	**0.029**
	65-75	13535	0.95 (0.92-0.99)	**0.012**	
	>75	4769	-	-	
Percent No High School Degree Quartiles 2000	>= 29%	5785	1.02 (0.98-1.05)	0.303	**0.027**
	20 – 28.9%	8395	0.97 (0.94-1.00)	**0.045**	
	14 – 19.9%	9061	1.01 (0.98-1.04)	0.398	
	< 14%	16403	-	-	
Urban/Rural 2003	Metro	33677	0.92 (0.85-1.00)	**0.046**	0.106
	Urban	5244	0.92 (0.85-0.99)	**0.035**	
	Rural	723	-	-	
Distance	<= 5 miles	11870	0.96 (0.93-0.99)	**0.004**	**0.003**
	5 - 10 miles	9678	0.95 (0.93-0.98)	**0.002**	
	10 - 15 miles	5674	0.95 (0.92-0.98)	**0.002**	
	> 15 miles	12422	-	-	

			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
Charlson-Deyo Score	0	33362	1.00 (0.94-1.08)	0.890	0.155
	1	5224	0.97 (0.91-1.05)	0.488	
	2	1058	-	-	
Pathologic T	T1	27623	1.06 (0.99-1.13)	0.110	0.166
	T2	10967	1.04 (0.97-1.11)	0.259	
	T3	1054	-	-	
Pathologic N	N0	27446	0.98 (0.93-1.03)	0.387	**<.001**
	N1	8219	0.94 (0.88-0.99)	**0.027**	
	N2	2366	0.91 (0.85-0.97)	**0.005**	
	NX	1613	-	-	
Year of Diagnosis	2009	931	0.00 (0.00-0.00)	**<.001**	**<.001**
	2010	8635	0.00 (0.00-0.00)	**<.001**	
	2011	9450	0.03 (0.03-0.03)	**<.001**	
	2012	9873	0.16 (0.16-0.17)	**<.001**	
	2013	10755	-	-	

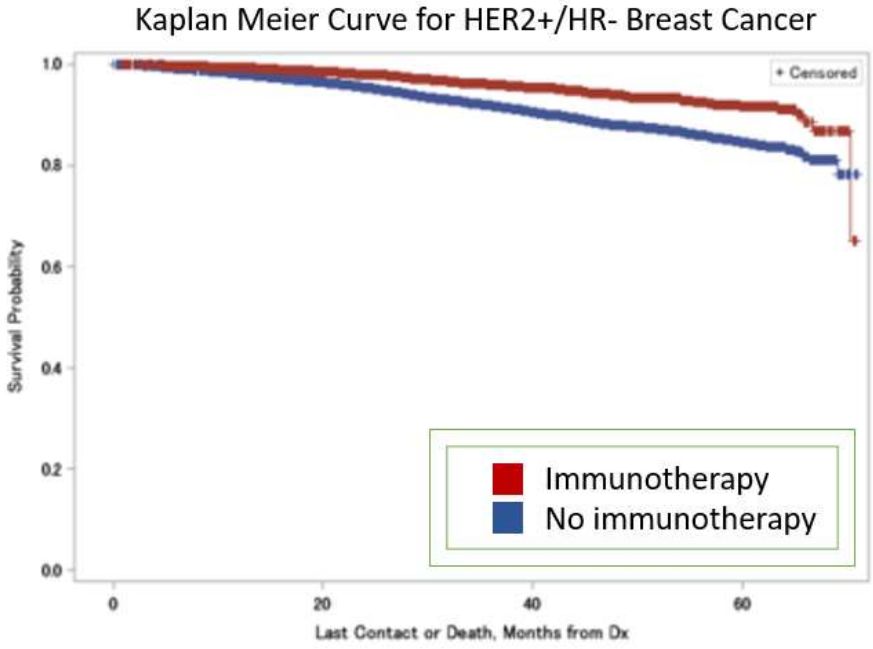
			Last Contact or Death, Months from Dx		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**

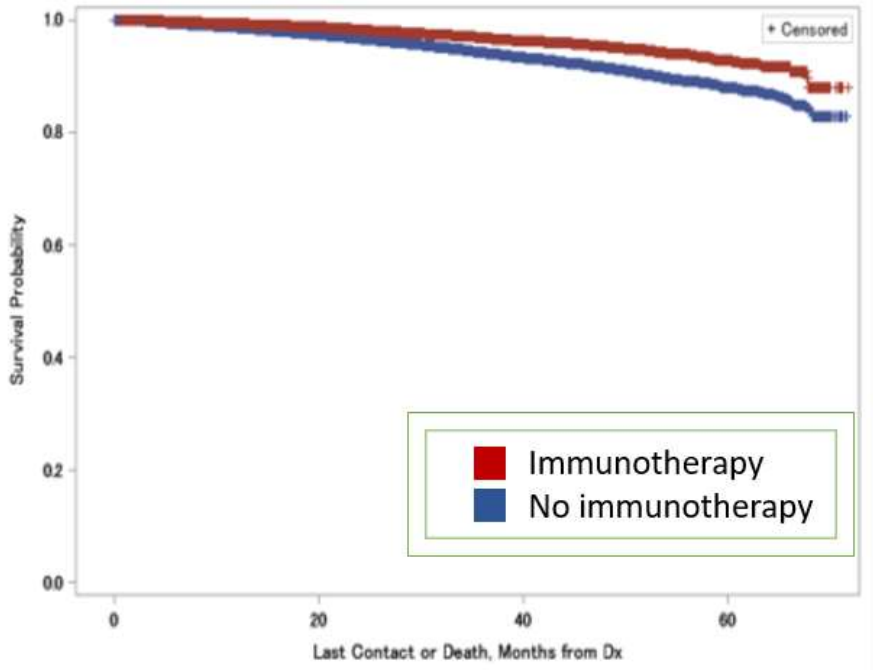
* Number of observations in the original data set = 39644. Number of observations used = 39644.

** Backward selection with an alpha level of removal of .20 was used. The following variables were removed from the model: Median Income Quartiles 2000, Insurance Type, and race_cat.

Figure 9: Kaplan Meier Curve Analysis for HER2+ Breast Cancer



A) HER2+/HR- Breast Cancer



B) HER2+/HR+ Breast Cancer

Discussion

We investigated the relevant factors associated with immunotherapy receipt in the United States using the NCDB from 2010 – 2013. The factors that lead to immunotherapy treatment varied and ranged from patient characteristics, treatment facility characteristics, socioeconomic status, and tumor-related factors. Overall, the rate of compliance was 38.24%, which was lower than the rates seen in prior studies examining immunotherapy initiation. Vaz-Luis et al. reported a trastuzumab compliance rate of 55.6% in their study of SEER data from 2010-2011 [91]; Reeder-Hayes et al. found a 50% compliance rate in white women and 40% compliance in African Americans from 2010-2011 [92]. The ASCO guidelines for use of trastuzumab in breast cancer patients was published in 2010 [38], and these findings suggest that there is widespread underuse of trastuzumab in eligible patients. Encouragingly, treatment concordance increased from 24.34% in 2010 to 69.80% in 2013, demonstrating significant improvement in immunotherapy receipt for patients with early stage invasive breast cancer. It is also possible that as time progressed, more and more treatment centers increased their documentation of immunotherapy use in the NCDB.

We found that concordance with immunotherapy treatment in eligible patients resulted in a significant risk reduction in mortality of 50% in HER2+/HR- patients and 40% in HER2+/HR+ patients. This finding is in line with prior literature regarding mortality and disease-free survival associated with the initiation of trastuzumab in HER2+ eligible breast cancer patients [93]. Other sources have cited reduction in mortality ranging from 37% to 51% seen in clinical trials [88, 89].

We found that younger patients were more likely to receive immunotherapy if recommended by evidence-based guidelines. This is a long-standing pattern observed in systemic breast cancer treatment studies [92]. Patients who are older can have significant competing mortality risks that preclude them from receiving the survival benefits seen with targeted immunotherapy. Recent population-based

analyses have suggested that there is higher rates of cardiac toxicity among older patients treated with trastuzumab [94]. However, research has demonstrated that healthy older patients do not receive the recommended guideline concordant care [95]. The significant benefit of immunotherapy may be underrecognized in this patient population by physicians wary of its potential side-effects such as cardiotoxicity, and it should be an option given the right context of life quality and life expectancy [96].

Facility factors also played a role in receipt of immunotherapy, where rates varied by both type of facility and geographic location. Facilities in the South, West, and lower volume institutions such as community cancer centers were more likely to under use immunotherapy. These geographic differences have been seen in other studies [71-73] examining breast cancer treatment and needs to be addressed as it has a significant impact on breast cancer outcomes.

Other studies examining trastuzumab compliance have seen significant racial differences in usage [91]. Our analysis was mixed in this regard. While white patients had a significant increase in compliance compared to black patients in HER2+/HR- cancers, this effect was not seen in the HER2+/HR+ cancer. The only socioeconomic factor that was determined to be predictive of immunotherapy concordance was insurance status. Eligible patients with private insurance were more likely to receive immunotherapy when it is guideline recommended compared to patients with no insurance or government insurance (Medicare or Medicaid). Treatment disparities associated with insurance status has been well documented elsewhere, and the stage at presentation of breast cancer in women with no insurance and government insurance is significantly worse than those with private insurance [97].

Concordance with immunotherapy treatment in eligible patients resulted in a significant risk reduction in mortality of ~50% in HER2+/HR- patients and ~40% in HER2+/HR+ patients. This underscores the need to offer and ensure access to immunotherapy for eligible patients, including

making referrals to high volume treatment centers, in order to provide the best care and offer the best chance of survival. While the overall survival benefits seen in this study may be secondary to a combination treatment effect rather than immunotherapy alone, other studies have demonstrated the benefit of immunotherapy in other settings [88, 90].

There are several limitations to this study. NCCN guidelines exclusively recommend trastuzumab for treatment, while ASCO guidelines suggest several other immunotherapy drug options such as pertuzumab [67, 90]. The NCDB does not document the specific name of the drugs used in the patients; therefore, there is no way to ascertain the exact drug regimen for the patient. In addition, it is unknown whether patients finished the full regimen of trastuzumab immunotherapy or not; the NCDB only documents the initiation of such treatments. It is also possible some immunotherapy treatments were misclassified; it is known that treatment data can be incorrectly reported in large, retrospective databases [98]. It should be noted that the criteria for immunotherapy coding in the NCDB has changed over the course of the study. Starting in 2013, six drugs, (alemtuzumab/campath, bevacizumab, rituximab, trastuzumab, pertuzumab, and cetuxumab), previously classified as chemotherapy were reclassified under immunotherapy. This may explain why our initial treatment compliance rate sharply increased in 2013 to 69.80% when previously it started as 24.31% in 2010, in addition to increased compliance and documentation of these therapies by treatment centers.

Nonetheless, the high number of patients in the NCDB and the capture of socioeconomic and facility level factors that are not in other databases are strengths of the study that allow us to elucidate important variables that are associated with guideline concordant care as well as assess national practices in complying with established clinical guidelines.

Overall Conclusion

This is one of the first studies examining early stage breast cancer practice patterns on a national scale using the NCDB. We consistently found several patient, facility-level, tumor, and socioeconomic factors that were associated with receipt of guideline concordant care in early stage breast cancer. For example, we consistently found that older patients were significantly less likely to be compliant in all areas of treatment examined. On explanation of this is that the benefit of treatment may be underrecognized in the older patient population due to the wariness of potential side-effects. This should be addressed as we and others have shown that there are significant negative effects to noncompliance, and previous studies have demonstrated that when older patients receive equal treatment, they exhibit equal outcomes compared to younger patients. In addition, insurance status is also a major influence in treatment compliance in our study. It has been shown in regional studies that patients with private insurance have significantly higher odds of receiving recommended treatment compared to government and no insurance. In particular, a study conducted using the California Cancer Registry noted that patients without private insurance had 16-25% lower odds of receiving treatment compared to private insurance holders [99]. There may also be underlying factors associated with not having private insurance, such as poor family support and less physician follow-up that result in poorer outcomes.

Interestingly, race was not consistently associated with receipt of guidelines concordant care. Racial disparities in guidelines-concordant care have been previously reported, but out studies indicated that lack of access (e.g. insurance), rather than race or ethnicity, was the main driver for disparities in this regard. Once chemotherapy is offered, virtually all chemotherapy patients, regardless of race, accepted and received treatment. Optimizing care to target patients with risk factors that lead to

nonadherence to guidelines concordant care will help ensure that they comply with the recommended treatments.

Evidence-based guidelines exist to guide care, but compliance rates with such guidelines, even among academic or high-quality centers, vary dramatically. An important need exists to inform clinicians regarding the associated outcomes and promote guideline adherence among oncology providers across all types of treatment centers. We also noted that lower volume institutions ,such as community cancer centers and comprehensive community cancer programs, were less likely to adhere to guideline concordant therapy and may be associated with worse overall survival among patients. Specialization seen in high-volume institutions has been linked as a successful approach to enhance treatment techniques and improve outcomes [100]. With the growth of multisite health care delivery organizations, concentrating volume in fewer locations may benefit survival outcomes in the long run.

Small, often single institution, studies have shown that guideline concordant care can improve survival [44-46, 101]. These NCDB analyses are among the first large studies using national data to demonstrate a significant survival advantage when treatment is compliant with evidence-based guidelines. Optimizing care to target patients with risk factors that may lead to nonadherence to guideline concordant care –may help ensure better compliance and thus better outcomes. Compliance with these guidelines leads to decreased mortality. Following guidelines doesn't just improve quality of care, it improves the most essential outcome, overall survival. With the newer emphasis on value-based care, it is important we address these discrepancies in treatment and prevent the higher risk of survival reduction due to lack of guideline concordant therapy. This study reflects the tumor stages most amenable to treatment, with participating hospitals likely administering higher quality of care compared to non-participating hospitals. Thus, it is likely the disparity estimates are conservative relative to non-participating institution.

The advantages of the database are numerous, including a very large sample size for all sub-analysis groups, diverse patient population, and fairly generalizable results across the U.S. Due to the large patient population, we assumed that any missing data was missing completely at random. This allowed us to use complete case analysis and exclude any missing data entries while still giving us sufficient power to arrive at our conclusions. In addition, the NCDB contains outstanding clinical/pathological data with the inclusion of variables that measure patient education, income levels, and patient area of residency. This allows the inclusion of socioeconomic factors in our univariate and multivariate analysis that is not possible with other national datasets.

While large sample size is a strength of the study, one issue is that it is extremely easy to reach significance for all the variables. Because of this, we were careful in selecting only the variables that had been validated by several other studies to address the questions in our specific aims. For example, insurance status, education level, income level are all variables that have been used in other studies as markers of socioeconomic status [102-104]. In addition, many of our findings (with the notable exception of the significance of race) reported similar findings as seen with other regional and smaller-scale studies that used similar variables. Finally, most of our results had a p-value was less than .001; there was much higher standard for significance compared to the widely-used significance test of $p = 0.05$. Another limitation of the dataset is that the primary outcome for these patients was overall survival, not cancer-specific survival. For a disease such as breast cancer, where patients may live 20+ years after diagnosis, overall survival may not be the optimal measure for disease-specific outcome related to treatment decisions. Coding in the dataset is also an issue. From the inception of the database in 2004 to present, data entry practices have changed. An example of this is seen in the immunotherapy analysis where six drugs were reclassified in 2013. Other limitations include missing data, and lack of real-time follow up.

Future directions include the construction of a risk stratification system based on the covariates we have identified to be most significant in predicting treatment compliance. In addition, propensity score matching will be included in the papers submitted for publication.

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