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The Tri-State Experience: Outcome Analysis of Patients with Triple Negative Breast Cancer Treated at Marshall University

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The Tri-State Experience

Outcome Analysis of Patients with Triple Negative Breast Cancer Treated at Marshall University

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Abstract

Breast cancer is the most frequently diagnosed malignancy in women in the United States. It is the second most common malignancy to cause death, with approximately 39,000 women dying of breast cancer in the United States in 2013.

Triple negative breast cancer is defined as the absence of estrogen, progesterone and human epidermal growth factor receptor 2 receptors. It has been associated with a higher incidence in African American women, a younger age and a more advanced stage at diagnosis, and an inferior overall survival.

To recognize the differences of our West Virginia community population when compared to the national average, we conducted a retrospective review of all patients diagnosed with breast cancer from 2000-2012.

Introduction

Breast cancer is the most frequently diagnosed malignancy in women in the United States.[1] There were 232,340 women diagnosed with breast cancer in 2013. This accounts for 29% of new cancer cases. It is the second most common malignancy causing death with 39,620 women dying of breast cancer in the United States in 2013.[2]

A breast cancer tumor is characterized by the presence or absence of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2). These biomarkers have a predictive and prognostic value in the course of treatment. Triple negative breast cancer (TNBC) is defined as the absence of all three receptors and accounts for 10-20% of the newly diagnosed breast cancers globally.[3]

Triple negative breast cancer has also been associated with racial disparities. African American women are found to have a higher incidence of TNBC when compared to Caucasian and Hispanic women (OR 2.98, 95% CI 2.12-4.20).[4-5] Women diagnosed with triple negative disease tend to be of younger age (34% were 18–29 years of age), lower socioeconomic status, and are more obese when compared to hormone positive tumors (ER/PR+, HER2 negative).[4-5]

Triple negative tumors have been found to have distinct features when compared to non-triple negative cancers including: larger in size, higher nodal positivity, higher advanced stages, more lympho-vascular invasion and higher percentages of poorly differentiated tumors.[5-6] These tumors have also been shown to have an inferior cancer-specific and overall survival (OS) with the highest risk of death within the first two years after diagnosis (breast cancer-specific survival: HR 8.30; 95% CI, 6.23-11.05) (OS: HR 6.10; 95% CI, 4.81-7.74).[7] Women with triple negative tumors are more likely to have higher rates of visceral metastases, brain metastases, lung and loco-regional metastases, but have been found less likely to have bone metastases.[7]

To understand the differences of our Tri-State community population (West Virginia and it's neighboring states Kentucky and Ohio) compared to the national average, we conducted a retrospective review of all patients diagnosed with breast cancer from 2000-2012. Our goal was to assess the differences and survival outcomes between triple negative breast cancer and all other types of hormone positive disease in our community-based hospital practice.

Methods and Data Review

This is a retrospective chart review of patients diagnosed with breast cancer at Marshall University/Cabell Huntington Hospital from 2000-2012.

The purpose was to assess the differences in survival and stage at diagnosis among hormone positive (ER/PR positive), HER2 positive, Triple Positive (ER/PR/HER2 + and ER/HER2 +), and Triple Negative disease (ER/PR/HER2 negative) in a 12 year period. Patient information was accessed through our hospital Breast Cancer Registry Database. Data collected included tumor hormone status, age of the patient at diagnosis, race, family history of breast cancer, stage of tumor at diagnosis, date of diagnosis, year the patient was deceased or if the patient is still alive at date of last contact, and treatment if applicable. Patients with DCIS, LCIS, missing pathology and hormone status were excluded.

The time interval between the date of diagnosis and date of death or last contact was calculated in days. Each individual pathology report was verified for hormone status and diagnosis of breast cancer. The patients were divided into 4 groups: Hormone Positive (ER/PR positive), HER2 positive, Triple

Table I – Number of Breast Cancer Patients Separated by Hormone Status

Hormone Status	Number of Patients (%) N=1022
Hormone Positive (ER or PR Positive)	735 (71.9)
Triple Negative	144 (14.1)
Triple Positive (including ER/HER2 Positive)	88 (8.6)
HER2 Positive	55 (5.4)

Positive, and Triple Negative for analysis. Patient characteristics were assessed for stage at diagnosis, family history of breast cancer, and survival. Local disease was defined as Stage I and Stage II, regional disease as Stage III and metastatic disease as Stage IV. Local disease included Stage I and II disease together due to their similar treatment regimens, and overall survival. The primary endpoint was a two and five year overall survival by hormone/HER2 receptor status among the four groups.

Results

This retrospective review included 1,022 patient charts from 2000-2012 that were diagnosed with breast cancer at Cabell Huntington Hospital. Seventy two percent of the patients were hormone positive (ER/PR positive), while 14% of the population was diagnosed with triple negative disease (Table I). Seven hundred and ninety patients presented with local disease (Stage I+II), 111 with regional disease (Stage III), 74 with metastatic disease (Stage IV) and 47 had missing information. Thirty percent of the African American population was diagnosed with triple negative disease (9/30) in comparison to only 14% of the Caucasian population (134/983). A large proportion of African Americans were also diagnosed with HER2 positive disease (13%) versus only 5% of the Caucasian population (Table II). SEER database information from 1995-2009 documents that the incidence rate of breast cancer was found to be the highest in the United States in Kentucky (523.1/100,000 patients) with West Virginia and Ohio not too far behind (496.8/100,000 and 470.8/100,000 patients respectively).[2]

The median age at diagnosis for triple positive disease was 53 years old, while the median age at diagnosis for triple negative, hormone positive and HER2 positive were 58 years old, 60 years old and 60 years old, respectively. When comparing our patients to a nearby facility (West Virginia University - WVU), the mean age at diagnosis was 51.7 years old for the triple negative hormone group versus 58.2 years old in the other hormone combination groups.[8]

Patients in each group reported a significant family history of breast cancer in a first degree relative, ranging from 62% in the

Table II – Patient Characteristics by Race and Hormone Status

Hormone Status	Caucasian	African American	Other	P Value
N (%)				Fisher's Exact Test = 0.04
Hormone Positive (ER/PR +)	714 (72.6)	14 (46.7)	7 (77.8)	
Triple Negative	134 (13.6)	9 (30)	1 (11.1)	
Triple Positive (including ER/HER2+)	84 (8.6)	3 (10)	1 (11.1)	
HER2 Positive	51 (5.2%)	4 (13.3)	0 (0)	

Table III – Patients Reporting a Family History of Breast Cancer, Triple Negative vs. Non-Triple Negative

Family History of Breast Cancer	Triple Negative	Non-Triple Negative	Pearson Chi Square Test P = 0.10
Number (%)			
Yes	109 (75.7)	60 (68.2)	
No	31 (21.5)	22 (25)	
Missing	4 (2.8)	6 (6.8)	

HER2 positive group to 76% in the triple negative group. Using a Pearson Chi-Squared test, patients presenting with triple negative breast cancer were compared to non-triple negative disease showing no correlation between family history and the incidence of TNBC (p value = 0.10) (Table III).

We were unable to identify the number of patients and their race by state distribution at our institution. Data reviewed from WVU also did not delineate patients by race or state distribution. The population of the Tri-State area at our institution consisted mostly of Caucasian females (Table II). However, the rate of African American patients diagnosed with triple negative disease was significantly higher when compared to the Caucasian population (30% vs. 13.6%, respectively; p value = 0.04). This demonstrates that our population of African American females presented with a more aggressive disease subtype at initial diagnosis.

Overall survival (OS) was evaluated and results adjusted by stage and hormone/HER2 status (Figure I). Stage IV breast cancer was associated with the worst overall survival at just under 25% alive at 5 years (p value <0.001). Subset analysis revealed that survival was also drastically decreased at 2 years for our patients diagnosed with Stage IV disease, either HER2 positive or triple negative, at time of presentation (26.7% and 32.3% respectively). This poor overall survival was in comparison to all other hormone groups and existed despite early diagnosis and early stage at presentation (p value <0.001 for both groups) (Figure II). When evaluating the five year overall survival for the triple negative disease group versus all other hormone/HER2 groups with local disease (Stage I+II) and regional disease (Stage III), there was a significant decrease in survival for the TNBC group at each stage (p value 0.03 and 0.02 respectively) (Figure III).

The unadjusted overall mortality of triple negative breast cancer patients when calculated by the Cox Regression Model was significantly increased (HR of 1.803, CI 1.289 – 2.52; p = 0.001). When adjusted for stage and age at diagnosis, TNBC patients were found to be 2.1 times more likely to die of their disease when compared to all other hormone/HER2 groups (p value < 0.0001; CI 1.455-2.936). In comparison, triple negative breast cancer patients studied in the National Comprehensive Cancer Network group showed an OS hazard ratio of 2.72 (p <0.0001) after adjusting for age, stage, race and other tumor factors.[7]

Discussion

Triple negative breast cancer (TNBC) is a challenging clinical condition. Systemic therapy for these patients is limited to conventional chemotherapy due to the lack of hormone and HER2 receptors. In this regional retrospective data analysis, TNBC patients were compared to non-TNBC patients to identify the disparities and outcomes among each group.

Triple negative breast cancer occurred in 14% of the study population with a similar rate reported in another article published by West Virginia University.[8] African Americans with breast cancer represented only 3% of our study population. This demonstrates the demographic difference of our region when compared to national data by the Centers for Disease Control and Prevention, which reported that African Americans represent about 14% of the population with breast cancer.[9] Despite such an underrepresented population in this study, TNBC had a higher prevalence in the African American group (30% or 9/30) when compared to other non-triple negative breast cancer groups. This observation was consistent with a California cancer registry review published by Amirikia et al.[10], which revealed that African Americans developed the highest

Figure I. *Five Year Overall Survival by Stage of Disease at Diagnosis*

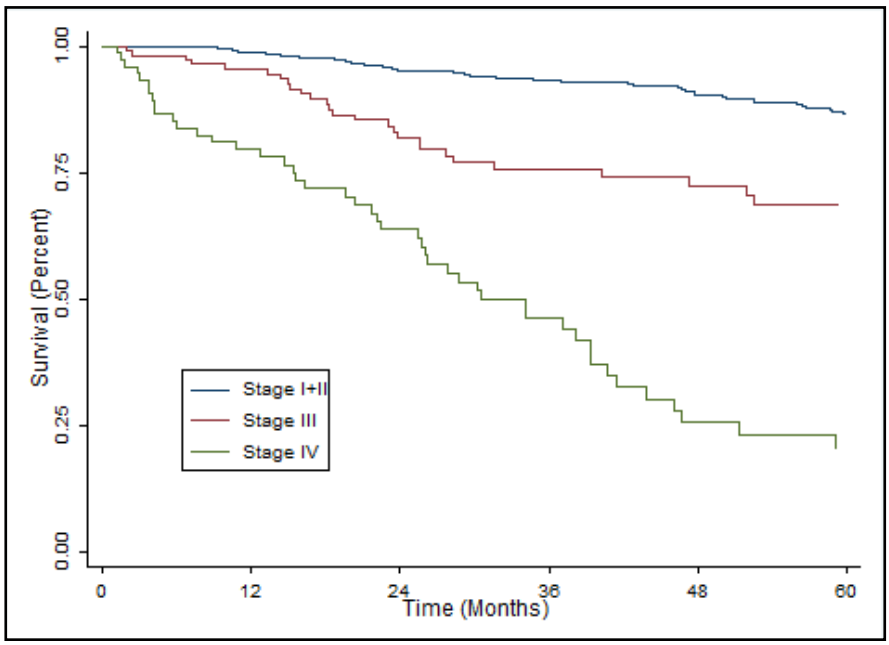
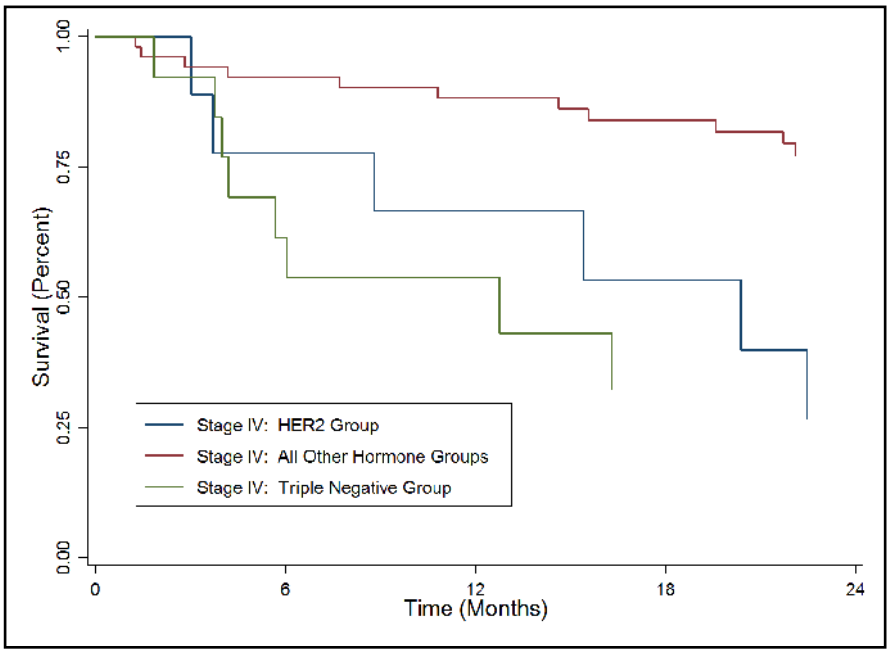


Figure II. *Two Year Overall Survival for Stage IV Disease by Hormone Group*



rate of triple negative disease when compared to Hispanics and Caucasians at all age groups.

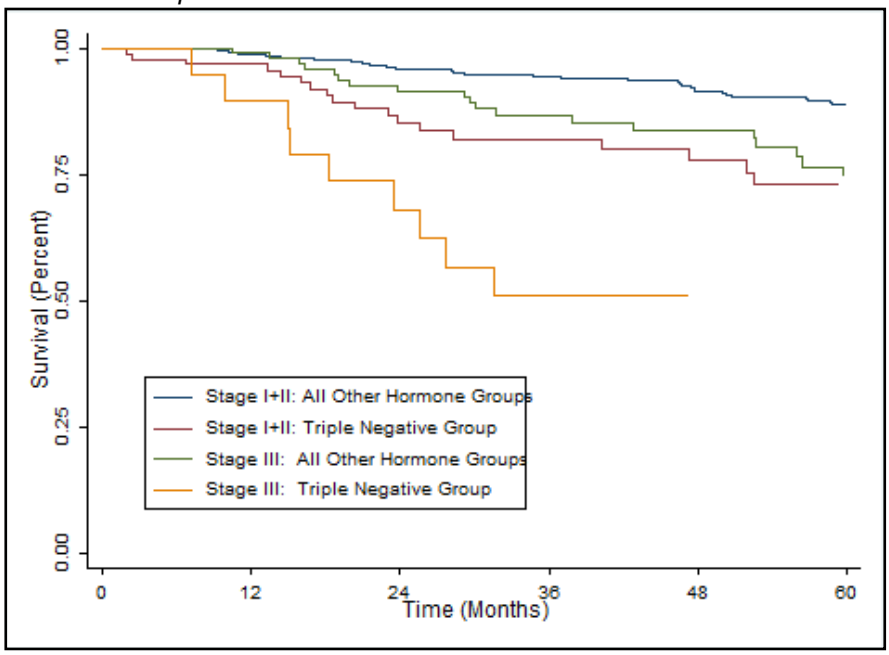
Contrary to other reports[4-5,11], the women with triple negative disease in our study had a non-statistically significant lower median age at diagnosis when compared to the hormone positive (ER/PR +) and the HER2 + only groups (58 years old and 60 years old, respectively). Furthermore, triple positive (ER+/PR+/HER2+ or ER/HER2+) patients had a median age at diagnosis that was lower than the TNBC patients (53 years old versus 58 years old). When comparing these results to other institutions in West Virginia, our triple negative breast cancer patients are presenting at a later age on average when compared to other women diagnosed with triple negative breast cancer at other facilities (58 years old vs. 51.7 years old).[8] A probable explanation for this disparity may be due to the small sample size of this study.

Family history is a well-known risk factor for breast cancer. Among all groups in our study, a positive family history was reported at higher rates when compared with a study by the Collaborative Group on Hormonal Factors in Breast Cancer, which reported a family history of breast cancer between 7-12%.[12] The rate of positive family history of breast cancer in our triple negative patient population was 75.7%. Despite having a significant proportion of patients with a family history of disease, there was no correlation between triple negative disease and a positive family history as documented by a Pearson Chi Square test (p=0.10). BRCA mutational status was not analyzed due to lack of reporting in the Tumor Registry database.

Studies by Dent et al and Lin et al reported a more advanced stage of disease at diagnosis (i.e Stage IV) for triple negative breast cancer patients when compared to other hormone groups.[6-7] Even though TNBC has been reported to be more aggressive, our study revealed that our triple negative breast cancer population presented at the time of diagnosis with more local disease (Stage I+II – 74%) rather than advanced disease (Stage III or IV – 22%). This finding may be related to campaigns for breast cancer screening and good surveillance by physicians and patients in the area, especially in those whom a family history is known.

The two year overall survival in early stage breast cancer patients (Stage I+II) was similar among all hormone positive groups, with triple negative and HER2 positive only disease being slightly lower at 91.6% and 88.5%, respectively. Multiple reviews have confirmed that TNBC patients have an overall inferior outcome.[5-7, 10] The Stage IV

Figure III. *Five Year Overall Survival for Local and Regional Disease by Hormone Group*



triple negative breast cancer group in our study had an overall poorer outcome when compared to the other hormone positive groups ($p < 0.001$), but not when compared to the HER2 positive only group. However, when comparing the HER2 positive group to all other hormone groups (excluding triple negative disease), the overall survival was inferior for the HER2 positive group (p value of <0.001). The study by Amirikia et al documented a worse overall survival at 5 years for African Americans when compared to Caucasian females (117 months vs. 166 months; $p < 0.001$).[10] The worse OS found in our retrospective review may be related to environmental factors, socioeconomic status and ability to reach adequate care. Patients in the Tri-State area sometimes travel great distances (up to 3 hours) to reach the hospital for care.

Multiple studies from the 1990s have documented a decrease in response rate to endocrine therapy and chemotherapy in patients who were hormone positive (ER/PR+) and also HER2 positive.[13-15] In vitro studies performed found that higher levels of the c-erbB2 proto-oncogene associated with the HER2 receptor status promoted resistance to endocrine therapy and/or chemotherapy and may have contributed to less than expected results from anti-HER2 therapy.[14-15]

Major limitations of this report were that it was a retrospective study with a small number of patients.

Conclusion

Consistent with national data, the overall survival outcome of patients with triple negative breast cancer in our rural population was inferior when compared to patients with hormone positive disease, however the OS of the triple negative hormone group was not as poor as the national data (OS hazard ratio 2.07 vs. 2.72, respectively). This likely is due to the small number of patients included in this review.

The higher incidence of triple negative breast cancer in our African American female population was also consistent with national data. In contrast, the higher incidence of family history and advanced stage of disease at diagnosis did not correlate with the incidence of triple negative breast cancer in our retrospective study. Patients in this study had a higher degree of family history of breast cancer and presented at an earlier stage at time of diagnosis likely due to effective screening and patient awareness.

Further studies are warranted to discover more effective therapy for this poor outcome population of breast cancer.

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