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Impact of Germline *BRCA* Mutation Status on Survival in Women with Metastatic Triple Negative Breast Cancer

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Abstract: Purpose: To investigate the association between germline deleterious *BRCA1* or *BRCA2* mutations (g*BRCA*+) and overall survival (OS) for patients with metastatic triple negative breast cancer (mTNBC). Methods: An IRB approved prospective multisite registry enrolling stage I-IV TNBC patients from 2011-2018 was utilized. Demographics, treatments, genetic results, recurrence and survival were collected. OS was estimated according to the Kaplan-Meier method and compared between groups (g*BRCA*+and *BRCA* wild type, wt) by log-rank test. Cox regression model was used for univariate and multivariate analysis of factors associated with risk of death. Results: 100 patients with mTNBC were enrolled on the registry between 2011- 2018. For 100 patients, 20% (20/100) had *de novo* stage IV whereas 80% (80/100) had metastatic recurrence. 12% had g*BRCA*+ status; 72% were g*BRCA* wt type; and 16% had unknown g*BRCA* status. g*BRCA*+ patients were younger (49 vs. 57 years, p=0.02) but otherwise well matched to g*BRCA* wt including similar metastatic disease burden and prior treatments. No patients received a PARP inhibitor. With 31 months median follow-up, median overall survival was 21 months (95% CI [13-23] months) for all patients, 18 months (95% CI [15-27] months) for g*BRCA* wt patients and has not yet been reached for g*BRCA*+ patients (p=0.023). 3-year estimated OS is 63% in g*BRCA*+ versus 28% in g*BRCA* wt (p=0.02). On multivariate analysis, g*BRCA*+ was associated with reduced risk of death (HR=0.33; 95%CI [0.23-0.91], p=0.033). Conclusions: In patients with mTNBC g*BRCA*+ patients have a clinically significantly improved 3-year OS compared to g*BRCA* wt patients. Further research is needed to understand tumor and host biological reasons for this observation. As these patients are at risk for primary site progression and secondary breast and ovarian cancers, further research regarding the role of proactive surgical treatment in mTNBC with g*BRCA* mutation is warranted.

Keywords: Breast Cancer, BRCA, Metastatic, Triple Negative

1. Introduction

Triple negative breast cancer (TNBC) accounts for 15% of all diagnosed breast cancers. [1] Interestingly, TNBC patients have a higher chance of carrying a deleterious *BRCA* germline mutation (g*BRCA*+) (15-20%) versus the general population of breast cancer patients. [2] It is well established that g*BRCA*+ are at elevated risk for initial and secondary breast cancers as well as ovarian cancer. Risk reducing mastectomy (RRM) is recommended for most

gBRCA+ patients to lower their risk of developing an initial breast cancer, and bilateral mastectomy is typically recommended for patients with unilateral breast cancer if they are known or found to be g*BRCA*+ at the time of cancer diagnosis. [3, 4] While appropriate surgical intervention is necessary for all breast cancer patients to achieve optimal outcomes, even the best surgery cannot combat the biology of the disease.

Unfortunately for TNBC patients, the risk of recurrence, including metastatic recurrence, is high (20-40%) and usually observed within the first 3 years following original diagnosis. [1] The median overall survival (OS) for metastatic TNBC (mTNBC) is short (9-12 months) but there is significant heterogeneity for individual patients. [5, 6] While modern systemic treatment advances such as poly ADP ribose polymerase inhibitors (PARPi) are associated with improved OS in g*BRCA*+ mTNBC patients, these medications only add 3-5 months survival on average. [7, 8] Furthermore, there are no currently available biomarkers that can identify those mTNBC patients with better prognosis. In addition, it is unclear whether g*BRCA* status is associated with differences in OS for mTNBC patients.

Thus the authors aimed to evaluate the impact of g*BRCA* mutation status on survival in women with mTNBC.

2. Methods

2.1. Patients

An IRB approved multisite prospective registry was founded in 2011 to enroll TNBC patients presenting for treatment at an academic cancer center along several community oncology practice locations (NCT02302742). Eligible patients were women >18 years of age with stage I-IV TNBC (defined as estrogen receptor and progesterone receptor ≤10% by immunohistochemistry and lack of HER2 amplification/overexpression according to the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines). All patients signed written informed consent, per US Common Rule, and then were prospectively followed via the registry for disease status, recurrence, and survival. All treatment was at the direction of the patient's physicians. Of note, no patients enrolled in the registry received PARPi given the timing of the registry opening, timing of query, and overlap with standard of care systemic treatment.

For the purposes of this study, the prospective registry was queried for patients enrolled from 2011-2018 with a diagnosis of metastatic disease (either *de novo* or recurrent stage IV); these patients made up the current study population. Patients were further classified according to their g*BRCA* status, specifically germline deleterious *BRCA1* and/or *BRCA2* mutation carriers (g*BRCA*+) versus g*BRCA* wild type (*gBRCA* wt) patients. All of the patients underwent genetic testing per standard clinical practice using commercial tests.

2.2. Data Collection

Relevant data collected at the time of patient enrollment in the registry included demographics, family history, genetic testing results, cancer staging and cancer treatment. Enrolled patients were followed for breast cancer related events including local and systemic treatments, genetic testing results (if performed at a later date), disease status, recurrence (including site (s) and timing), and survival status.

2.3. Statistical Analysis

Descriptive statistics were analyzed using mean with standard deviation versus counts and percentages where appropriate. Differences between *gBRCA*+ carriers and *gBRCA* wt were assessed for baseline demographics and tumor data. Overall survival (OS) was defined as time from mTNBC diagnosis to death due to any cause. [9] OS was estimated according to the Kaplan-Meier method and compared for g*BRCA*+ versus g*BRCA* wt using log-rank test. Cox regression model was used for univariate and multivariate analysis of factors associated with risk of death; p-values as well as 95% CIs are reported from two-sided tests. P-values<0.05 were considered statistically significant. Multivariate analysis variables included age, T stage, lymph node status, receipt of metastatic chemotherapy, type of breast surgery, receipt of radiation, *de novo* disease status, g*BRCA* mutation status. All analyses were conducted using SPSS Statistics version 24 (IBM Corporation).

3. Results

3.1. Study Population and Demographics

From the 643 total patients enrolled between 2011 and 2018, 100 individuals (15.6%) were identified as having mTNBC and thus make up the current study population. Within this group, 12% (n=12) were g*BRCA*+, while 72% (n=72) were g*BRCA* wt and 16% (n=16) had unknown *BRCA* status. Patients with unknown g*BRCA* status or *BRCA* VUS (variants of uncertain significance) were included in g*BRCA* wt group.

The median age at diagnosis of metastatic breast cancer was 55 years, with g*BRCA*+ being younger than g*BRCA* wt patients (49 vs. 57 years old, p=0.008). Patients most commonly were Caucasian (76%) or African American (17%). Most patients had T2 (46%) N0 (45%) grade III (85%) disease. g*BRCA*+ and g*BRCA* wt were well matched with respect to race (p=0.63), T stage (p=0.69), N stage (p=0.37), and grade (p=0.83). Table 1 details the study population and demographics data.

Table 1. *Patient Characteristics.*

Characteristics	Entire Population (n=100)	gBRCA wt (n=88)	gBRCA+(n=12)	p-value
Median Age at mTNBC (yr)	55 (25-86)	57 (25-86)	49 (30-63)	0.008*
Median Time from Primary Diagnosis to mTNBC (mo)	19 (1-118)	19 (1-65)	29 (4-114)	0.29
Race				
Caucasian	76 (76%)	66 (75%)	10 (83%)	
African American	17 (17%)	16 (19%)	1 (8%)	0.63
Asian	3 (3%)	3 (3%)	0 (0%)	
Other	4 (4%)	3 (3%)	1 (8%)	
T Stage				
1	28 (28%)	25 (29%)	3 (25%)	
2	46 (46%)	39 (44%)	7 (58%)	0.69
3	19 (19%)	17 (19%)	2 (17%)	
4	7 (7%)	7 (6%)	0	
N Stage				
0	45 (45%)	38 (43%)	7 (58%)	
1	39 (39%)	34 (39%)	5 (42%)	0.83
2	7 (7%)	7 (8%)	0	
3	9 (9%)	9 (10%)	0	
ER/PR				
0%	83 (83%)	71 (81%)	12 (100%)	0.21
1-10%	17 (17%)	17 (19%)	0	
Histological Grade				
I	1 (1%)	1/78 (1%)	0	0.83
II	12 (14%)	10/78 (13%)	2/11 (18%)	
III	76 (85%)	67/78 (86%)	9/11 (82%)	
LN Status at Diagnosis of Primary Disease				
Positive	55 (55%)	50 (57%)	5 (42%)	0.37
Negative	45 (45%)	38 (43%)	7 (58%)	
De Novo mTNBC				
Yes	20 (20%)	16 (18%)	4 (33%)	0.25
No	80 (80%)	72 (82%)	8 (67%)	

*statistically significant.

3.2. Metastatic Disease and Treatment

A majority of patients (n=80) had metastatic disease recurrence with fewer (n=20) having *de novo* stage IV breast cancer. Visceral metastasis (84%) were most common followed by bone only (12%) and extra-axillary lymph node involvement (4%). A majority of patients received chemotherapy in the metastatic setting (86%) with most receiving 1-2 lines (66%). g*BRCA*+ and g*BRCA* wt were well matched with respect to timing of metastatic diagnosis (*de novo* versus recurrent, p=0.25), location of metastasis (p=0.67), and lines of chemotherapy in the metastatic setting (p=0.62). There were 13% of patients who did not receive chemotherapy for their metastatic disease (either recurrent or *de novo*). Of those, 7 patients received radiation only and 6 patients were in palliative care.

For patients with recurrent stage IV disease, surgical management at the time of original non-metastatic diagnosis included 59% (n=47/80) mastectomy, 35% (n=28/80) lumpectomy, 43% (n=34/80) sentinel lymph node biopsy, 61% (n=49/80) axillary dissection. 57% (n=16/28) of patients received radiation after lumpectomy, and 43% (n=20/47) patients received post-mastectomy radiation. Type of surgery and radiation administered at original diagnosis were similar in g*BRCA*+ and g*BRCA* wt patients who had metastatic recurrence.

For patients who were *de novo* stage IV, 50% (10/20) had local treatment at some point of time in their treatment history including surgery only (n=4), radiation only (n=3), and surgery plus radiation (n=3). Analysis by g*BRCA* status for this subgroup was not performed due to the small number of patients.

A small subset of patients had surgery (n=4), radiation (n=22) or surgery plus radiation (n=3) to address their metastatic disease site. Receipt of surgical and/or radiation treatment to the metastatic site was similar for both g*BRCA*+ and g*BRCA* wt groups (p=0.77).

Table 2 details the metastatic disease characteristics and treatments.

Table 2. *Metastatic Disease Characteristics and Treatments.*

Characteristics	Entire Population (n=100)	gBRCA wt (n=88)	gBRCA+(n=12)	p-value
Site of Metastatic Disease				
Lymph Node Only	4 (4%)	4 (5%)	0	0.67
Bone Only	12 (12%)	11 (12%)	1 (8%)	
Visceral	84 (84%)	73 (83%)	11 (92%)	
Metastatic Chemotherapy*				0.64
Yes	83/96 (86%)	75/85 (87%)	9/11 (82%)	

Characteristics	Entire Population (n=100)	gBRCA wt (n=88)	gBRCA+(n=12)	p-value
No	13/96 (96%)	11/85 (13%)	2/11 (18%)	
Lines of Chemotherapy				
0	13 (13%)	11 (12%)	2 (17%)	
1 to 2	66 (66%)	58 (66%)	8 (67%)	0.62
3 to 4	9 (9%)	9 (7%)	0	
>4	6 (6%)	5 (6%)	1 (8%)	
Unknown	6 (6%)	5 (6%)	1 (8%)	
Local Treatment for mTNBC				
Radiation Only	23 (23%)	19 (22%)	4 (33%)	
Surgery Only	4 (4%)	3 (3%)	1 (8%)	0.77
Radiation and Surgery	3 (3%)	3 (3%)	0	
None	70 (70%)	63 (72%)	7 (59%)	

*metastatic chemotherapy information unavailable for 4 patients.

3.3. Overall Survival (OS)

At a median follow-up of 31 months, median OS for all patients was 21 months (95% CI [13-23] months). Median OS for g*BRCA* wt (18 months, 95% CI [15-27]) was significantly lower than that for g*BRCA*+ (not yet reached) (p=0.023) 3-year estimated OS is 28% in g*BRCA* wt versus 63% in g*BRCA*+ (p=0.02). (Figure 1) On multivariate Cox regression analysis, g*BRCA*+ status was associated with reduced risk of death (HR=0.33, 95% CI [0.23-0.91], p=0.033), as was receipt of chemotherapy in the metastatic setting (HR=0.11, 95% CI [0.05-0.23], p<0.001). (Table 3) As previously noted, no patients received PARPi.

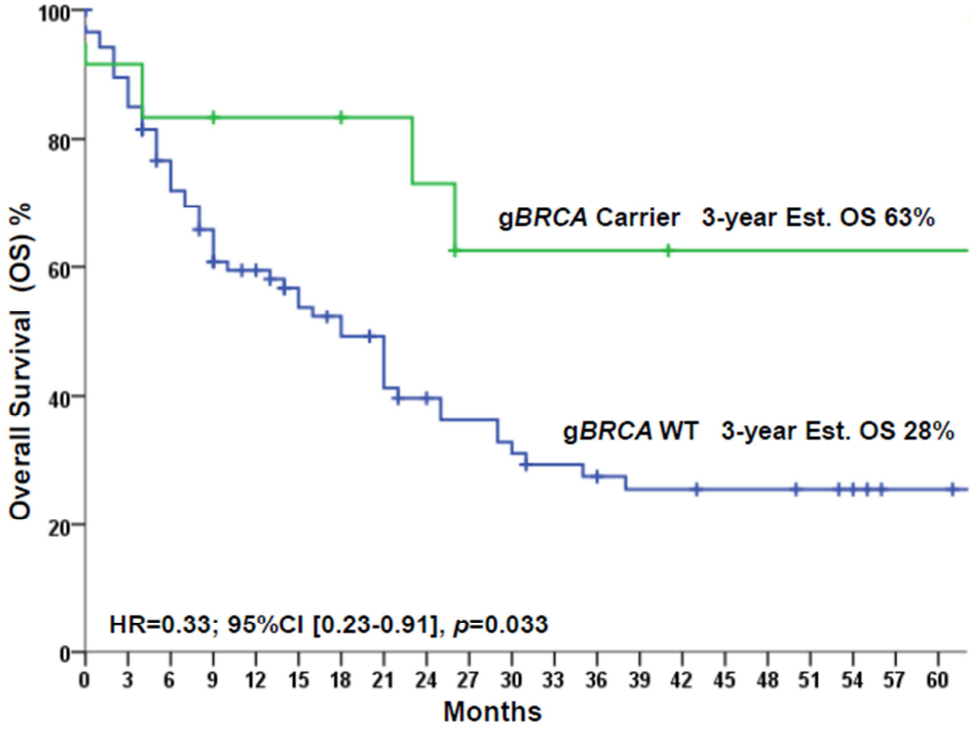

Figure 1. *Overall Survival by gBRCA status.*

Table 3. *Univariate and Multivariate Analysis.*

Univariate Analysis of OS			
Variable		HR (95% CI)	p-value
De Novo	No	1	0.19
	Yes	0.62 (0.31-1.26)	
gBRCA+	No	1	0.033*
	Yes	0.33 (0.23-0.91)	
Metastatic Chemotherapy	No	1	<0.001*
	Yes	0.21 (0.11-0.40)	
Local Therapy	No	1	0.95
	Yes	0.98 (0.56-1.72)	
Visceral Disease	No	1	0.71
	Yes	0.41 (0.33-1.42)	

Univariate Analysis of OS			
Multivariate Analysis of OS			
gBRCA+	No	1	0.001*
	Yes	0.13 (0.04-0.44)	
Metastatic Chemotherapy	No	1	<0.001*
	Yes	0.11 (0.05-0.23)	

*statistically significant.

4. Discussion

mTNBC patients with g*BRCA*+ have a significantly improved OS versus g*BRCA* wt patients (3-year OS 63% vs. 28%, p=0.02) which cannot be explained by demographics, cancer characteristics, metastatic disease characteristics, or cancer treatments and persists upon multivariate analysis. As mTNBC is associated with poor OS with no available biomarkers that can identify those patients with better prognosis, our study is novel in that it is the first to correlate g*BRCA*+ status with improved survival in these individuals. Furthermore, this data is clinically important as these patients are at risk for local disease progression as well as secondary breast and ovarian cancers, underscoring the need for further research on the role of ongoing screening, prophylactic, and primary site (breast/axillary) surgery.

Current National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for stage IV patients with HER2 negative tumors as well as for patients <60 years of age with TNBC at any stage.[10] These recommendations are based on the higher likelihood of a patient with TNBC having an underlying genetic mutation versus patients with other receptor profiles, as well as consideration for systemic therapy which may be impacted based on genetic testing results. [10] Recent data indicating that PARPi use improves OS on the order of months in patients who are g*BRCA*+ in both the metastatic and non-metastatic settings has made a significant impact on patient care. [7, 8] The difference in survival in our study cannot be attributed to PARPi, as no patients received PARPi given the time of patient enrollment in the registry versus the time of mainstream medication availability. Thus as PARPi use increases in practice, it is reasonable to hypothesize that the survival benefit for g*BRCA*+ mTNBC patients seen in our study will become even more pronounced.

According to current national guidelines, patients with metastatic breast cancer are not routinely offered breast and axillary surgery, particularly in mTNBC where the OS has historically been low. [11] While multiple publications have recently reported some improvement in OS who have primary site surgery, the exact patients who benefit and best time of surgery remain unclear. [12-16] Prior publications have neither stratified patients according to genetic testing status nor reported their genetic testing results. Based on the findings in our study which demonstrate improved OS (63% at 3 years), mTNBC patients who are g*BRCA*+ may be ideal candidates for primary site surgery in the metastatic setting particularly if they demonstrate upfront metastatic disease stability. With up to 36% of patients requiring some primary site surgery to control local regional progression, there is at minimum anticipated benefit to breast and axillary surgery in terms of progression-free survival (PFS) for the g*BRCA*+ patients in our study. [17] The impact on OS remains unclear, but will hopefully be clarified as results of additional trials of surgery in the metastatic setting become available.

As patients with mTNBC have improvement in OS based on systemic therapy developments, they also face additional challenges. One key factor is the role of routine screening and preventative treatments in the setting of metastatic cancer. g*BRCA*+ patients without a cancer diagnosis are offered increased screening due to their elevated lifetime risk of breast cancer. [10] Those who develop breast cancer are advised to consider bilateral mastectomy as their risk of subsequent breast cancer is up to 30% over their lifetime. [18] The risk that a g*BRCA*+ patient with mTNBC would develop a new breast or ovarian cancer during their time receiving treatment for metastatic disease is unknown. As systemic therapy advances and patients are living longer with mTNBC, the risk of secondary cancers, role of screening, and role of prophylactic surgery are important to consider This consideration is particularly true in g*BRCA*+ patients who are at high risk for developing additional malignancy, but also have longer OS compared to *gBRCA* wt patients, based on the results of our study.

There are some limitations to our study that should be considered. First, the study population is very specific and thus there are small numbers of patients included. This research is difficult to conduct on a national level as typical large datasets would not contain information on genetic testing results, systemic therapy, and other potential confounding variable that were considered in the present analysis. Going forward, multisite registries that can appropriately collect and organize this information as well as including genetic testing results in national trials will be beneficial in assessing our results on a larger scale. Second, reasons for improved survival in g*BRCA*+ patients are not clear. Further research may provide insight into novel molecular pathways which differ between g*BRCA*+ and g*BRCA* wt patients that contribute to the OS advantage noted. Future publications assessing PFS and OS in metastatic breast cancer should consider including genetic testing information in results as genetic status may be an important factor in who may or may not benefit from primary site surgery.

5. Conclusions

g*BRCA*+ mTNBC patients have a clinically significant improvement in 3-year and median OS compared to g*BRCA* wt mTNBC patients. With the addition of PARPi to g*BRCA*+

treatment regimens, OS in these patients is likely to improve, conferring a greater survival advantage in the metastatic setting. Further research is needed to understand tumor and host biological reasons for this observation. As these patients are at risk for primary site progression and secondary breast and ovarian cancers, our findings also underscore need for further research regarding the role of proactive surveillance and surgical treatment in mTNBC g*BRCA*+ patients.

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