Patterns of Failure in triple negative breast cancer patients in an urban, predominately black population

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Abstract

Background: We sought to evaluate the comprehensive patterns of failure associated with treatment for triple negative breast cancer (TNBC) at a single urban institution. Methods: A retrospective review of TNBC patients treated from 2005-2015 was conducted. Detailed patient, tumor and treatment characteristics were included. Information on patterns of treatment failure, including local, regional, distant and combinations of these three were collected. Chi-square testing was used to compare variables, while logistic regression with Kaplan-Meier estimate was used to calculate overall survival (OS) and freedom from recurrence (FFR). Results: With a median follow-up of 46 months, 32 (16%) documented failures occurred. Locoregional failures comprised 84% of failure patterns whether isolated or in combination with distant failure. 5-year OS and FFR were 76.4% and 83.8%, respectively. On univariate analysis, treatment failure was associated with insurance type, smoking status, presence of LVSI, clinical detection of tumor, increasing clinical tumor size (>2 cm), and increasing pathologic tumor stage, nodal stage, and overall staging. On multivariate analysis, pathologic nodal staging was the most significant predictor of treatment failure. Conclusion: Our work shows that with modern therapies, treatment outcomes for patients with TNBC are very good. 53% of patients failed in distant and locoregional sites simultaneously, with an additional 34% failing locally only. These results highlight the need for aggressive local therapies in high-risk patients as well as suggest a need for improved follow up care focusing on detecting locoregional failures. Integrated multidisciplinary care is essential in the management of these patients at time of failure. Keywords: Triple negative, breast cancer, failure, patterns, predictors

Background

Triple negative breast cancers (TNBC) account for approximately 12-17% of all breast cancers in the United States, and behave more aggressively than hormone-receptor positive breast cancers [1-3]. These tumors are negative for estrogen-receptor (ER), progesterone-receptor (PR) and human epidermal growth factor receptor 2 (HER-2) and tend to occur more commonly in black women and women <40 years old [4-5]. 20% of triple negative breast cancer patients will have a BRCA mutation present [6]. The vast majority of TNBC are in the basal-like subtype as defined by gene expression profiling [7].

These cancers tend to present aggressively with rapid growth and are diagnosed clinically more often than radiographically [5]. Patients have improved disease-free survival with the addition of neoadjuvant chemotherapy, especially in the locally advanced setting [8-10]. However, TNBC tumors generally relapse earlier after standard chemotherapy regimens and have a higher tendency for visceral and soft tissue involvement when metastasized [11]. Death within two years of diagnosis is much higher for women with triple negative breast cancer, though this recurrence rate starts to plateau when women with triple negative breast cancer survive longer than two years [5,12]. Moreover, patients who do not achieve pathologic complete response (pCR) have a poorer outcome relative to patients with receptor positive disease [11].

To date, most studies evaluating patterns of failure have treated failure patterns as discrete entities consisting of local, regional, or distant metastases [12-14]. However, locoregional recurrence is often under-reported when distant metastases are found. Locoregional recurrences can cause significant morbidity and decreased quality of life for patients. As such, we sought to evaluate the comprehensive patterns of failure associated with treatment for triple negative breast cancer at a single urban institution. With this information, we hypothesized that further understanding of patterns of failure could inform future treatment directions and follow up paradigms based upon the most likely site of failure.

Methods

Patient selection:

After institutional review board (IRB) approval, a health insurance portability and accountability act (HIPAA) compliant retrospective database was constructed to include all patients with triple negative breast cancer who completed their initial evaluation including pathologic diagnosis and all subsequent treatments at our institution between January 1, 2005 and December 31, 2015. Patients were included if they had a diagnosis of invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC) with ER, PR and Her-2 receptor proven negative by immunohistochemistry (IHC) or fluorescence in-situ hybridization who received chemotherapy, surgery, and/or radiation therapy at our institution. ER , PR, and Her-2 negativity was considered as <1% IHC expression [15-16]. Other histologies included metaplastic (n=1) and anaplastic carcinoma (n=1). Exclusion criteria included patients any positivity (>1%) in ER or PR, or Her-2 amplification, patients receiving treatment outside of our institution, final pathologic diagnosis of a non-breast primary origin, and any patient with DCIS histology without an invasive component.

Patient characteristics collected included age at diagnosis, sex, race, marital status, zip code (a surrogate for income), insurance status, BMI, smoking status, smoking pack-years, age at menarche, age at menopause, gravida, parity, oral contraceptive use, hormone replacement, HIV status, diabetes status, BRCA mutation status, and cardiovascular disease or risk factors. Tumor characteristics included histology, tumor location, radiographic or clinical detection, AJCC 7^{th} edition clinical and pathologic tumor (T) stage, T size (cm), clinical and pathologic nodal (N) stage, metastatic (M) stage, overall clinical and pathologic stage grouping, histology, Ki-67 (%), overall grade, and presence or absence of lymphovascular space invasion (LVSI).

Patterns of Failure

For all patients who developed a disease failure on the basis of imaging (CT or PET) and/or biopsy, we collected information on patterns of treatment failure, including local, regional, distant and combinations of these three (local and regional, local, regional, and distant, local and distant, and regional and distant). Documented sites of first failure and distant failure sites were included. Local

failure was defined as a failure within the breast or chest wall. Regional failure was defined as any failure in the axilla, supraclavicular lymph node basins or internal mammary lymph node chain.

Treatment:

Medical and surgical oncology data included chemotherapy type, neoadjuvant versus adjuvant chemotherapy administration, dose reductions in chemotherapy, surgical procedure (lumpectomy vs mastectomy) and axillary assessment (sentinel lymph node vs axillary dissection), and pathology response (i.e. complete, partial, or no response).

Radiation oncology data included total radiation dose in Gy, dose per fraction, technique of treatment delivery, treatment volumes (breast/chest wall vs comprehensive nodal irradiation), dose and volume (dose volume histogram data) for the heart and lungs, and acute and late toxicities of treatment.

Statistical Analysis:

Categorical variables are presented as numbers (percentages) and continuous variables are presented as medians with ranges. Univariate and multivariate analysis were used to assess for prognostic clinicopathologic factors, and chi-square testing (Pearson's) was used to assess for differences between failure and non-failure groups. Logistic regression with Kaplan-Meier estimate was used to calculate overall survival (OS) and freedom from recurrence (FFR). A p-value <0.05 was considered statistically significant. All univariate variables that were significant were entered into a forward conditional multivariable analysis to correct for any confounding variables. All analyses were performed using SPSS Statistical Software (Version 21, IBM Corporation).

Results

Patient and tumor characteristics

A total of 197 women met inclusion criteria, with a median age of 54 years (range 22-86). Race was predominantly black (64%), 41% were married, and 64% of patients treated had private insurance. Comprehensive patient, tumor and treatment characteristics stratified by failure status are outlined in Table 1.

In total, thirty-two patients (16%) in our cohort experienced treatment failure. Insurance type (p=0.002) and active smoking (p=0.002) differed between the two groups, but race and marital status were not found to be significantly different between the patients who failed treatment and those who did not (p=0.36 and 0.94, respectively). The tumor histology was predominately (99%) IDC, the vast majority (85%) were grade 3, and LVSI was present in 28% of patients. Clinical (self-palpation) detection occurred

in 73% of women. On Chi-square testing, presence of LVSI (p=0.036) and the method of tumor detection (p=0.003) were both significantly different between failure and non-failure groups. Grade and histology were not associated with an increased risk of treatment failure in our patient cohort (p=0.19 and 0.37, respectively) (Table 1).

According to AJCC 7th edition, the most common clinical stage was II (47%), followed by stage I (32%). Prevalence of failure increased with increasing stage: 15% in stage I, 18% in stage II, and 24% in stage III patients. Of patients who failed treatment, 28% were stage I, 47% were stage II, and 25% were stage III.

There was a significant difference in pathologic staging between those who failed and those who did not fail treatment (p<0.001). Largest tumor size was also documented and was stratified into 2 cm and 2 cm. Forty-nine percent of tumors were 2 cm, and increasing tumor size was significantly associated with treatment failure (p<0.001). Pathologic tumor stage was significantly different between the two groups (p=0.005); 35% of pT3/T4 patients failed compared to only 16% of pT1/T2 patients. Pathologic nodal stage was highly prognostic (p<0.001) with 36% of treatment-failure patients having either pN2 or pN3 pathologic nodal status compared to only 8% of the non-failure group.

Treatment

Almost all patients (95%) underwent surgical resection with lumpectomy performed in 53% of patients. Rates of sentinel lymph node biopsy and axillary dissection were not different between groups (p=0.76). Thirty-one percent of women received neoadjuvant chemotherapy while 63% of women received adjuvant chemotherapy. Adjuvant radiation was given in 62% of patients to a median dose of 60 Gy (range 10.8-70.4), and there was no difference in failure for those receiving <60 Gy (p=0.14). Radiation treatment modality (3D-CRT vs IMRT) did not differ between those who failed and did not fail treatment.

Patterns of Failure

Table 2 outlines comprehensive details for the 32 patients who failed treatment including site and pattern of failure, as well as subsequent treatments rendered. Patterns of failure in our TNBC cohort were varied and complex. The largest proportion of patients (53%) failed in distant and locoregional sites simultaneously, whereas 34% of patients developed local breast or chest wall recurrence only. Of those patients who had any distant failure, median OS was 23.5 months. Failure patterns did not differ by race (p=0.41). The most common sites of failure were the lungs (28%), followed by the liver (25%), bone and brain (22% each). Eight patients (25%) received further surgery for locoregional recurrences, while 17 (53%) received salvage chemotherapy at the time of relapse. The most common salvage chemotherapy regimens included carboplatin/gemcitabine, eribulin, and ixabepilone. Median OS from time of initiation of treatment for all patients who failed was 30 months while median OS from time of failure for these

patients was 8 months. Black patients had a median OS of 32 months compared to 23 months for white patients, but this was not significant (p=0.23).

Survival

Median follow-up for our entire cohort was 46 months (range 1-353 months). The median, 2-year and 5-year overall survival (OS) for the entire cohort was 45 months, 86.3% and 76.4%, respectively (Figure 1). Median, 2-year and 5-year freedom from recurrence (FFR) was 16 months, 88.1% and 83.8%, respectively (Figure 2). Median, 2- and 5-year OS rates for the patients who did not fail treatment was 46 months, 93.3% and 86.7%, respectively. Median, 2- and 5-year survival rates for patients with documented failures was 30 months, 55.4% and 35.3%, respectively. (log rank p<0.001 comparing OS of failure vs non-failure patients) (Figure 3).

Univariate/Multivariate Analysis

On univariate analysis, insurance status was associated with treatment failure (p=0.048). Specifically, patients with private insurance were significantly less likely than uninsured patients (OR 0.068, 95% CI 0.006-0.810, p=0.033) or Medicare patients (OR 0.051, 95% CI 0.004-0.699, p=0.026) to experience failure. We also found smoking status had a statistically significant impact on treatment failure (p=0.011), with current smokers more likely to experience treatment failure than nonsmokers at the time of TNBC diagnosis (OR 5.212, 95% CI 1.950-13.929, p=0.001) (Table 3).

In terms of tumor characteristics, presence of LVSI (OR 2.566, 95% CI 1.043-6.309, p=0.04) and clinical detection (OR 6.944, 95% CI 1.597-30.206, p=0.01) were associated with treatment failure. Increasing pathologic tumor stage (p=0.020), pathologic nodal stage (p=0.001), and overall pathologic stage (p<0.001) were also associated with treatment failure. In addition, patients with tumor size 2cm had significantly higher rates of failure (OR 6.996, 95% CI 2.293-21.342, p=0.001). Treatment modalities including receipt of chemotherapy (both neoadjuvant and adjuvant), type of surgery, and radiation therapy dose were not found to be associated with an increased risk of treatment failure (Table 3).

On MVA, pathologic nodal staging was most strongly associated with treatment failure (p=0.017). Pathologic N2 stage, specifically, had a significant association with treatment failure (OR 25.0, 95% CI 3.454-180.972, p=0.001) (Table 4).

Discussion

In our retrospective analysis of TNBC patients treated at the University of Maryland Greenebaum Cancer Center from 2005-2015, we found that 16% of patients failed treatment. All of our patients were women, predominantly black, and most underwent surgery and received anthracycline/taxane based

chemotherapy (neoadjuvant or adjuvant). Of the 16% of patients who recurred, 53% had distant and locoregional site failures simultaneously, whereas approximately 34% of patients developed local breast or chest wall recurrence only. Median and 5-yr overall survival for the entire cohort was 45 months and 76.4%, but only 30 months and 35.3% for those who suffered a recurrence. The median time to failure was 16 months. Factors found to be predictive of failure in our univariate analyses included insurance, smoking status, presence of LVSI, clinical detection (palpating a lump) of tumor, increasing clinical tumor size (>2 cm), and increasing pathologic tumor stage, nodal stage, and overall staging. When adjusted for covariates in MVA, increasing pathologic nodal staging was found to be the most significant predictor of treatment failure.

This rate of failure (16%) is consistent with other reported literature with rates ranging from 4-33.9% [12,14,17]. In addition, we found an isolated locoregional recurrence pattern rate of 7.6%. Review of literature found wide variability in rates of locoregional only recurrences (3-22%) in TNBC patients. This heterogeneity stems from both differences in retrospective patient populations as well as from differences in their treatment regimens [18-21].

TNBC tends to metastasize more frequently to viscera compared to hormone-receptor positive cancers [11]. In our study, we found the distant recurrence only rate was 16% (5/32). Visceral organs accounted for the primary site of first relapse in our analysis. The most common sites of distant failure in our study included the lungs (28%), liver (25%) and bone and brain (22%). This is consistent with two prior reports which both described lung metastases as the most common sites of failure in TNBC patients [14,22]. Specifically Kennecke found that of the patients with TNBC who had distant disease 42.8% had lung, 25.2% had brain, and 21.4% had liver metastases [22].

Other studies have reported distant recurrent rates of 16.9%-33.9% [12,17]. The cumulative distant recurrence rate in this cohort of failures was 53.1% (17/32), slightly higher than the earlier reported studies. Increased modalities to stage patients may account for the ability to detect both locoregional and distant metastases, especially with increased usage of PET/CT which has higher sensitivity and specificity in detecting distant metastases which may have been missed with less sensitive imaging techniques in the past [23-25]. Previous analyses studied patients from 1999-2008 [17] and 1987-1997 [12]. Of note, our 5-year freedom-from-recurrence rate was nearly 84%. While many of the previous studies had longer follow-up times than our study (46 months), the time for recurrence in TNBC is often within 1-3 years of diagnosis [3,12], so it is unlikely that our study significantly underreported recurrence rates. Dent et al. found that in non-TNBC cancers, the recurrence risk can continue to increase even after five years [12]. Consistent with this unique pattern of early recurrence, 21 (66%) and 24 (75%) of the recurrences in our analysis occurred within 2 and 3 years or treatment initiation, respectively. Interestingly, nearly 20% of our recurrences happened after 5 years, even though documented analyses suggest a reduction in recurrence risk after a few years of initially high risk of recurrence [11-12].

In terms of survival outcomes, our study found that the 5-year overall survival was 76.4%. Of those patients who lived longer than five years with TNBC, only 6/76 (7.9%) passed away from breast cancer,

with an additional 2 patients dying of other causes. For all patients who had disease recurrence, the median survival time was 30 months, decreasing to a median of 23.5 months in those with any distant failure. Some previously published data suggests that the median survival time for metastatic TNBC patients is roughly 12 months [5,26], which is much lower than our cohort. This may reflect improvement in systemic therapy options over time. Ovcaricek and Steward reported an overall 5-year survival of 74.5% [27] and 76.3% [17], respectively, which is in line with our reported survival. In the latter study, median time to recurrence was 18.8 months, similar to the median time to recurrence in our cohort (16 months).

In our retrospective analysis, we also wanted to elucidate potential socioeconomic, tumor, and treatment factors that could potentially predict recurrence risk. Nodal status, tumor size and LVSI are well documented prognostic tumor characteristics [27-29]. We corroborated these findings on UVA showing that all three of these tumor characteristics were statistically significant predictors of recurrence. In addition, because of our unique population in an inner-city with a predominantly black population, we also sought to better understand socioeconomic factors that could potentially predict those at higher risk of recurrence. TNBC is known to preferentially affect young black women, and these women often have poorer outcomes than white women [30]. Possible explanations for a race-based disparity in survival have been linked to lack of screening, socioeconomic status, access to insurance, and differences in treatment [31-32]. Interestingly, we found that the median overall survival of black patients was 50 months as compared to 31.5 months for white patients. In those who failed treatment, black patients had a median OS of 32 versus 23 months for white patients who recurred, though this was not statistically significant ($p=0.23$). These findings may reflect the higher proportion of black patients in our cohort which tend to be under-represented in studies.

Locoregional failure comprised 84% of failure patterns whether isolated or in combination with distant failure. This number is quite high and argues for the importance of locoregional therapy and possibly escalation of locoregional therapy for some patients. While death is typically caused by distant spread, locoregional disease can have a significant impact on morbidity and patient quality of life. For example, when women develop a dermal-lymphatic skin recurrence wound care is often required. Several publications have suggested a critical role of radiation therapy in TNBC. Wang et al. performed a randomized trial of women with anatomic stage I and II breast cancer who underwent mastectomy followed by chemotherapy or chemotherapy and radiation therapy [33]. Adjuvant chemotherapy and radiation therapy were associated with improved overall survival and recurrence free survival. Abdulkarim and colleagues performed a retrospective analysis of 768 patients treated at their center for TNBC [34]. At a median follow up of 7.2 years, they found that women with anatomic T1-2N0 TNBC treated with mastectomy +/- chemotherapy but no radiation therapy had increased risks of locoregional recurrence compared to the same women who elected breast conserving therapy with lumpectomy and radiation therapy suggesting an integral role of radiation therapy in the management of this disease. On the contrary, Dragun and colleagues found no difference in progression free survival and locoregional-free survival in their cohort of patients treated with and without radiation therapy during the first three years of follow-up [35]. These recurrence patterns provide an opportunity for escalation of therapy in high risk

patients such as addition of radiation therapy for all post-mastectomy TNBC patients, dose-escalation of radiation therapy or addition of chemotherapy during radiation therapy for patients.

Our data support prior work showing increased rates of locoregional failures in the TNBC patient population. Despite this body of data however, current follow up guidelines support breast only imaging in the lumpectomy setting (no systemic imaging) and no imaging in mastectomy patients or patients who have undergone reconstruction [36]. This data show increasing rates of recurrence by anatomic tumor stage as well as increasing pathologic T and N stage. 35% of patients with pT3/4 tumors experienced failure as did 47% of women with pN2/3 disease. We propose that these high recurrence rates warrant both breast/chest wall and systemic imaging. In most solid tumor sites, systemic or local imaging is performed when recurrence rates enter this range. Potential early detection of recurrence has the possibility to not only improve long term cancer outcomes but also allow for additional therapies and/or enrollment on clinical trials. Additionally, earlier detection of recurrence may also improve patient morbidity and quality of life outcomes.

Our study has some limitations, the first of which is the retrospective nature of our work. While we have meticulously maintained this database and incorporated as many potential clinical and demographic variables as available, it is possible that we may not have included all factors that could influence access to care and/or timely initiation of treatment and that could contribute to treatment failure. However, through a deep literature review we have incorporated the well-known factors associated with treatment failure in TNBC. Additionally, we have included a wide range of TNBC patients, which may include lower risk older women. However, our higher proportion of black women in this study who are higher risk likely balances out this difference. The relatively small number of patients in our cohort, and additionally our relatively low number of failures may decrease our power to detect factors associated with recurrence.

Conclusions

With modern BC therapies, we show good treatment outcomes for patients with TNBC, with 84% of patients free of disease at 5 years from initial diagnosis. The patterns of failure in TNBC are complex, with 84% of patients experiencing locoregional failure as a portion of their recurrence pattern but 53% of patients experiencing it combined with distant failure. Improvements in local and systemic therapies as well as follow up approaches including consideration of initial for (2-3 years) post diagnosis periodic re-staging are needed to allow for earlier detection of locoregional and systemic recurrence thereby improving morbidity and quality of life of patients with TNBC.

Abbreviations

3D-CRT: Three-dimensional conformal radiotherapy

AJCC: American Joint Committee on Cancer

CI: Confidence interval

ER: Estrogen receptor

FFR: Freedom from recurrence

Her-2: Human epidermal growth factor receptor 2

IDC: Invasive ductal carcinoma

IHC: Immunohistochemistry

ILC: Invasive lobular carcinoma

IMRT: Intensity-modulated radiotherapy

IRB: Institutional review board

LVSI: Lymphovascular space invasion

MVA: Multivariate analysis

OR: Odds ratio

OS: Overall survival

pCR: Pathologic complete response

PR: Progesterone receptor

TNBC: Triple negative breast cancer

UVA: Univariate analysis

Declarations

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee affiliated with the institutional review board of the University of Maryland Baltimore.

Consent for publication Not applicable

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Author's contributions HRC and SRR compiled and maintained the database and contributed equally to the writing of this manuscript. EMN provided valuable feedback prior to submission. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of enrolled patients.

Variable	
Age, years	54.5（35.0-73.0）
Gender	
Male	443 (80.3%)
Female	109 (19.7%)
Etiology	
Hepatitis B positive	446 (80.8%)
Hepatitis C	12 (2.2%)
Other	94 (17.0%)
ECOG score	
0	223 (40.4%)
1	329 (59.6%)
AFP, ug/mL	
Positive (>20)	441 (79.9%）
Negative (<=20)	111 (20.1%)
Total Bilirubin, umol/L	13.4 (6.3-32.7)
Albumin, g/L	38.0 (29.0-45.0)
Child-Pugh Grade	
A	451 (81.7%)
B	101 (18.3%)
Tumor number:	
Solitary	360 (65.2%)
Multifocal	192 (34.8%)
Tumor Size[a]	

≦5cm	118 (21.4%)
>5cm	434 (78.6%)
Vascular Invasion	
- Absence	35 (6.3%)
-Segmental portal vein	62 (11.2%)
-Lobar portal vein	188 (34.1%)
-Main portal vein	239 (43.3%)
-Hepatic vein/Inferior Vena Cava	28 (5.1%)
Hepatic regional lymph node involvement	
Absence	507 (91.8%)
Presence	45 (8.2%)

Note: Values are median (95% CI) or numbers (%).

ECOG score: Eastern Cooperative Oncology Group score; AFP: Alpha-Fetoprotein

[a]Tumor size was calculated as the maximum size of intrahepatic tumors

Table 2. Univariate and multivariate analysis for overall survival in patients with locally advanced stage HCC.

variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
gender	0.71	0.53-0.96	0.03			
Age (≧50/<50)	1.01	0.77-1.32	0.94			
HBV infection (presence/absence)	0.93	0.74-1.16	0.51			
ECOG score (0/1)	1.21	0.92-1.58	0.16			
AFP (≧400/<400)	1.33	1.02-1.72	0.03			
Child-Pugh grade (A/B)	1.16	0.86-1.56	0.33			
Tumor size (≧5/<5cm)	1.4	1.02-1.91	0.03			
Tumor number (Solitary/Multifocal)	0.95	0.73-1.24	0.72			
Vascular invasion[a]	1.19	1.04-1.37	0.01			
Lymph node involvement	0.84	0.53-1.33	0.47			
Treatment modality	0.75	0.65-0.87	<0.001	0.8	0.69-0.93	0.003

Note: HCC: hepatocellular carcinoma; HR: hazard ratio; CI: confidence interval;

HBV: hepatitis B virus; ECOG score: Eastern Cooperative Oncology Group score

AFP: Alpha-Fetoprotein;

[a]Vascular invasion type includes: absence of vascular invasion; segmental portal vein invasion, branch portal vein invasion, main portal vein invasion and hepatic vein/inferior vena cava invasion.

Table 3. Comparison of survival in patients receiving TACE alone versus TACE+Sorafenib before and after PSM analysis.

Estimated OS rates	TACE	TACE+Sorafenib	Log-rank P value
Before PSM	n=375	n=83	0.001
1-year	50.5%	73.7%	
3-year	29.8%	47.1%	
5-year	24.5%	34.9%	
Median OS	7.5 m	13.0 m	
After PSM	n=81	n=81	0.02
1-year	51.1%	74.8%	
3-year	36.2%	50.1%	
5-year	30.1%	38.4%	
Median OS	9.0 m	14.0 m	

Note: The Kaplan-Meier method was used to assess overall survival. OS: overall survival;

TACE: Transarterial Chemoembolization; HCC: hepatocellular carcinoma; PSM: propensity score matching

Table 3. Univariate analysis of variables with respect to treatment failure

Variable	Unadjusted		
	OR	95% CI	p-value
Race			0.756
White (REF)	-	-	-
Black	1.368	.591-3.168	0.464
Other	0	0	0.999
arriage Status			0.937
Iarried (REF)	-	-	-
Single	1.062	0.407-2.772	0.902
Widowed	1.056	0.303-3.676	0.931
Divorced	1.459	0.450-4.730	0.529
surance Status			**0.048**
insured (REF)	-	-	-
Private	0.068	0.006-0.810	**0.033**
Medicare	0.051	0.004-0.699	**0.026**
Medicaid	0	0	0.999
+ Supplemental	0.75	0.038-14.972	0.851
Other	0	0	0.999
noking Status			**0.011**
Never (REF)	-	-	-
Current	5.212	1.950-13.929	**0.001**
rmer (0-29 PY)	2.841	1.086-7.431	**0.033**
mer (>= 30 PY)	0	0	0.999
BMI			0.568
al Weight (REF)	-	-	-
Overweight	0.458	0.036-5.789	0.547
Obese	1.528	0.252-9.272	0.645
ECOG			0.467
0 (REF)	-	-	-
1	2.2	0.405-11.949	0.361
2	4.4	0.233-82.978	0.323
mor Location			0.929
(REF)	-	-	-
ght	1.16	0.543-2.477	0.701
teral	0	0	0.999
mogram Abnormality			0.845
r Outer (REF)	-	-	-
pper Inner	1.296	0.477-3.521	0.611
ower Outer	0.714	0.082-6.240	0.761
ower Inner	2.0	0.553-7.231	0.290

Method of Detection			
Radiographic (REF)	-	-	-
Clinical	6.944	1.597-30.206	**0.010**
Grade			0.255
1 (REF)	-	-	-
2	0.125	0.006-2.563	0.177
3	0.663	0.067-6.584	0.725
Ki-67			1.00
w Risk (<10%) (REF)	-	-	-
mediate Risk (10-19.9%)	0	0	0.999
High Risk (>= 20%)	0	0	0.999
LVSI			
Not Present (REF)	-	-	-
Present	2.566	1.043-6.309	**0.04**
Clinical T Stage			0.597
1 (REF)	-	-	-
2	1.269	0.471-3.421	0.637
3	1.385	0.321-5.971	0.663
4	3.0	0.621-14.494	0.172
Pathologic T Stage			**0.020**
1 (REF)	-	-	-
2	3.767	1.380-10.282	**0.010**
3	5.071	1.348-19.077	**0.016**
4	6.086	1.194-31.011	**0.030**
Largest T size (cm)			
<= 2 cm (REF)	-	-	-
> 2 cm	6.996	2.293-21.342	**0.001**
Pathologic N Stage			**0.001**
0 (REF)	-	-	-
1	3.172	1.093-9.204	**0.034**
2	16.1	4.148-62.485	**<0.001**
3	4.6	0.767-27.604	0.095

all Clinical Stage			0.734
I (REF)	-	-	-
II	1.164	0.473-2.865	0.740
III	1.813	0.625-5.265	0.274
IV	0	0	0.999

all Pathologic Stage			**<0.001**
I (REF)	-	-	-
II	2.976	0.948-9.343	0.062
III	13.138	4.022-42.916	**<0.001**
IV	0	0	0.999
oadjuvant Chemo			
No (REF)	-	-	-
Yes	1.38	0.627-3.037	0.424
Adjuvant Chemo			
No (REF)	-	-	-
Yes	1.631	0.707-3.763	0.251
Type of Surgery			
ectomy (REF)	-	-	-
lastectomy	0.901	0.416-1.955	0.793
lal Evaluation			
LND (REF)	-	-	-
ALND	1.131	0.512-2.498	0.761
dian RT Dose			
60 Gy (REF)	-	-	-
> 60 Gy	1.050	0.425-2.595	0.916

Table 4. Multivariate analysis of variables with respect to treatment failure

Variable	Adjusted		
	OR	95% CI	p-value
logic N Stage			**0.017**
0 (REF)	-	-	-
1	1.875	0.385-9.142	0.437
2	25.0	3.454-180.97	**0.001**
3	0	0	0.999

Figures

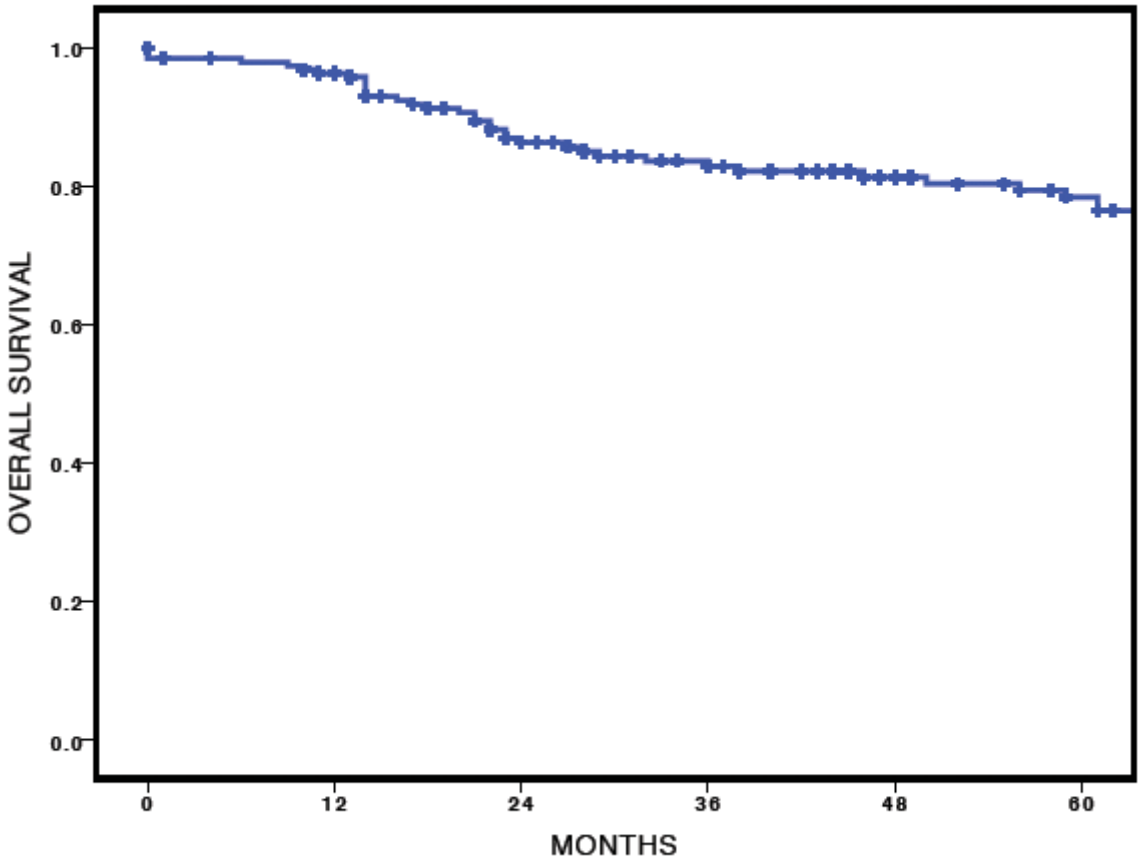

Figure 1

Kaplan-Meier curve illustrating overall survival for 197 patients with triple negative breast cancer

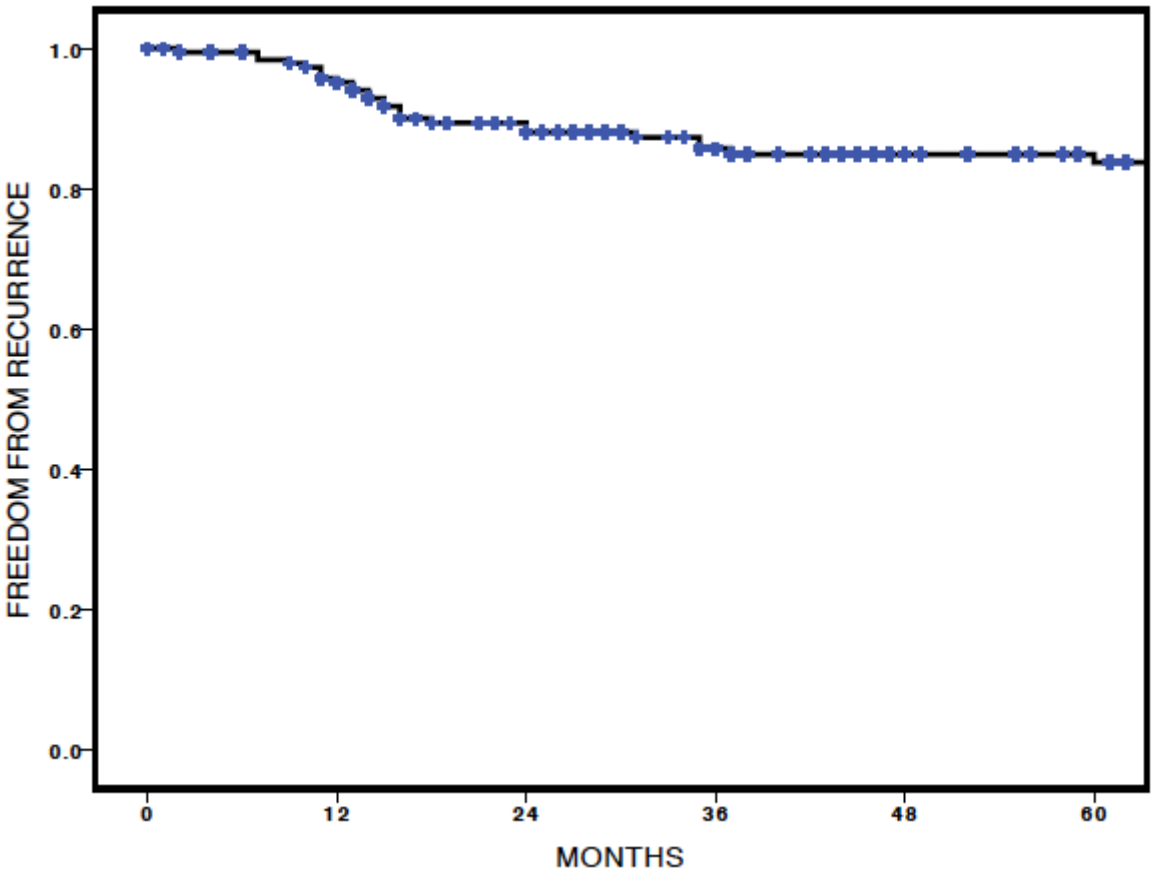

Figure 2

Kaplan-Meier curve illustrating freedom from recurrence for 197 patients with triple negative breast cancer

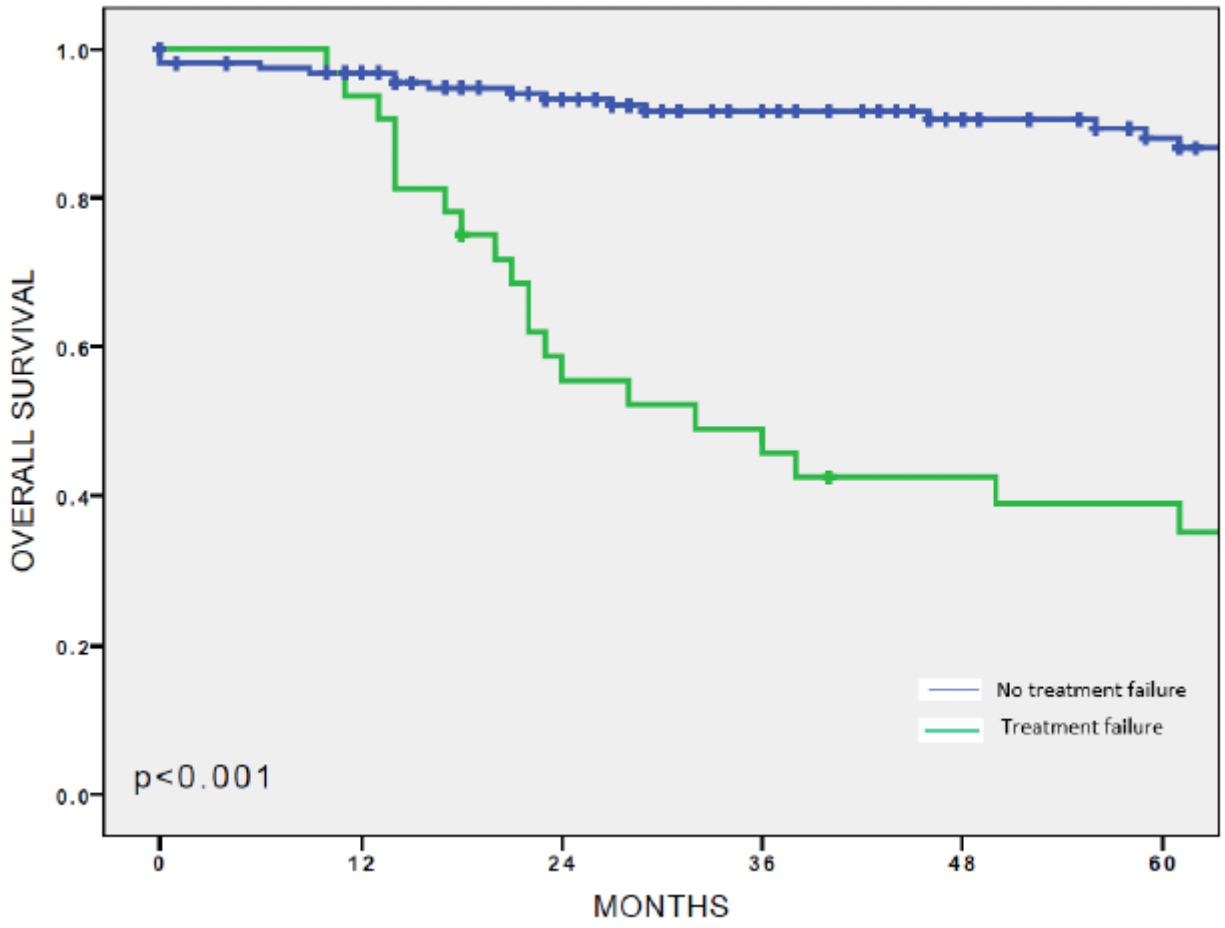

Figure 3

Kaplan-Meier curves illustrating overall survival of cohort stratified by those who failed (green) and those who did not fail initial treatment (blue) (log rank p<0.001)