Triple Negative Breast Cancer Patients Treated with Radiation Therapy: Improvement in Survival and Local Control With Adjuvant Chemotherapy Compared To Neoadjuvant Chemotherapy – A Hypothesis Generating Report

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Abstract

Background

Triple negative breast cancer (TNBC) (estrogen receptor (ER) – negative, progesterone receptor (PR) - negative, and human epidermal growth factor receptor 2 (HER2) -negative) is an aggressive subtype of breast cancer that is more common in younger women, carries a poorer prognosis and has a greater metastatic potential than receptor positive subtypes. Radiation therapy's ability to improve outcomes, especially the overall survival is controversial, more so among African American patients. The objective of this study is to evaluate local control and survival rates of TNBC patients treated with radiotherapy (RT) in our institution with a sizeable cohort of African American women.

Methods

This is a retrospective analysis of 67 TNBCs (2007–2017) at an academic state institution who underwent a lumpectomy and /or mastectomy (surgery) followed by adjuvant irradiation to a median total dose of 50 Gy (range 40.5–50.40 Gy). Chemotherapy was administered in a neoadjuvant (32) or adjuvant setting (35). For all 67 TNBCs, local control (LC), overall survival (OS), and disease-free survival (DFS) were estimated using the Kaplan-Meier method. The significance of survival variables was analyzed using the Cox univariate and multivariate proportional hazards model. A p-value of less than 0.05 was considered statistically significant. The SPSS 24.0 software was used for data analysis.

Results

The baseline characteristics of all 67 TNBCs were measured with median follow up of 58 months (range 10–142 months). Patients were stratified into two groups (neoadjuvant chemotherapy-RT (32) vs. adjuvant chemotherapy-RT (35)). The five-year rates for LC, DFS and OS were 14.8 % vs. 47.9 % (p = 0.002), 24.2% vs. 53.1 % (p = 0.015), and 65.1% vs. 92.2% (0.002) respectively. On Cox multivariate analysis, patients who received adjuvant chemotherapy were associated with statistically improved significant LC (p = 0.002) and OS (p = 0.002). The variables included were: BMI (p = 0.050), distance travelled (p = 0.027), 8th AJCC TNM staging (p = 0.018) and tumor grade (p = 0.022).

Conclusion

In this hypothesis-generating report, among TNBC patients undergoing RT, adjuvant chemotherapy appears to be better than neoadjuvant chemotherapy in determining the clinical outcomes.

Background
Breast cancer is the most common malignancy and a leading cause of cancer-related deaths in women [1, 2]. They are categorized by the presence or absence of three markers: estrogen receptors (ER), progesterone receptors (PR), and whether there is an overexpression of the encoded protein human epidermal growth factor receptor 2 (HER2). Triple negative breast cancer (TNBC) is defined as the absence of ER, PR, and a lack of HER2 overexpression [3]. TNBCs account for 10–20% of all breast cancer diagnoses; have the highest incidence among young and African-American women; and are frequently linked to breast cancer gene (BRCA) mutations [4, 5].

TNBC is notoriously aggressive and is known to be particularly sensitive to cytotoxic chemotherapy. However, despite being more responsive to chemotherapy, TNBC carries a worse prognosis than other breast cancer subtypes, highlighting the so-called “triple negative paradox” [6]. Compared to other breast cancers, patients with TNBC tend to relapse earlier (generally within 1–3 years after diagnosis), develop visceral metastases more often, and succumb to their metastatic disease more quickly (median survival rarely exceeds 12 months) [7].

Chemotherapy can play a vital role in both the adjuvant and neoadjuvant settings for patients with TNBC. Neoadjuvant chemotherapy is typically employed to downstage unresectable tumors, allowing for higher loco-regional control and breast conservative surgery rates, while adjuvant therapy is typically considered in patients with tumors at least 0.6 cm and in lymph nodes with any degree of malignant involvement [10, 12]. In the neo-adjuvant setting, pathological complete response (pCR) in TNBC patients has been shown to be a strong prognostic marker and using standard combinations of anthracycline, cyclophosphamide, and taxanes, 30–40% of women with TNBC are able to achieve a pCR [8, 9, 11].

In this article, we report the experience of our academic state institution in TNBC patients treated with tri-modality therapy, stratifying them by neoadjuvant versus adjuvant chemotherapy.

Methods

Study design and participants

This retrospective study includes a total of 67 TNBC women diagnosed and treated between 2007 and 2017 at the University of Mississippi Medical Center (UMMC), Jackson, Mississippi, USA. Institutional review board approval (IRB #2018 – 0218) was obtained and a browser-based database tool, research electronic data capture (REDCap) was used to gather and store the patient's information in password-protected computers. The written consent was waived due to the retrospective nature of the study and patient identifiers were removed before extracting the data. Out of the entire cohort of breast cancer, three hundred and nine with positive pathology staging, unknown tumor status, other races (other than Caucasians or African Americans), and ductal carcinoma in situ were excluded from the study so a total of 67 TNBC women were included in this analysis (shown in Fig. 1).
Epidemiological, clinical, demographic, treatment and outcome data were obtained from RedCap. The patients had all been stratified by treatment modality into TNBCs who received neoadjuvant chemo (32) and who received adjuvant chemo (35). The following patient’s characteristics were included: age, race, body mass index (BMI), tumor grade, and survival months. All data were collected, checked, analyzed, and interpreted by the postdoc research fellow (MN) and second-checked by the senior author (SV).

**Definitions**

Triple-negative breast cancer (TNBC) is cancer that tests negative for estrogen receptors (ER), progesterone receptors (PR), and excess human epidermal growth factor receptor 2 (HER2) protein. In other words, the growth of the cancer is not fueled by the hormones estrogen and progesterone, or by the HER2 protein. Disease-free survival (DFS), defined as the number that predicts the chances of staying free of disease or cancer after a particular treatment. Local control (LC), defined as the number that predicts the chances of staying free of cancer local recurrence after a particular treatment. Overall survival (OS), defined by the number of days from the date of initial diagnosis until the date of death/ the last contact. The censored cases are defined as the patients without death at the time of the last follow-up.

**Pathological Assessment**

Prior to the systemic therapy, pathological diagnosis, ER status, PR status, and HER2 status was determined by core biopsy. Tumors with less than 1% stained cells were considered to have negative ER and PR status. HER2 status was assessed by immunohistochemistry only if the results were 0 or 1+ staining and by fluorescence, in situ hybridization (FISH) confirmation if 2+ immunohistochemistry staining was present.

**Statistical Analysis**

The Pearson’s chi-square test is used to discover the relationship between two categorical treatment groups. Kaplan-Meier method was used to estimate the OS rates and the univariate significance of differences among survival curves calculated by the log-rank test. The co-variables associated with the OS, LC, and DFS were determined by the bi and multivariate Cox regression model. Hazards ratio (HR) was used to estimate time to event outcome with associated 95% confidence intervals (CIs) and P values ≤ 0.05 were considered statistically significant. Data were analyzed using SPSS 24.0 software (IBM, Armonk, NY, USA).

**Results**

**Patient Characteristics**

A total of 376 primary breast cancer patients treated at UMMC between 2007 and 2017 were identified. Out of 376 patients, 67 TNBC patients were included in this study; 32 (47.8%) were treated with neoadjuvant chemotherapy and 35 (52.2%) with adjuvant chemotherapy (shown in Fig. 1). The baseline characteristics of these patients (Table 1) had a median age of 59 years [y] (range, 35 to 77 y). African
American patients were presented in more numbers in both the treatment groups compared to Caucasians (83.6% vs. 16.4%; p = 0.408). TNBC patients treated with adjuvant chemotherapy were presented with higher BMI levels compared to patients treated with neoadjuvant chemotherapy (62.8% vs. 50.1%; p = 0.521). The patients in the adjuvant chemo group had higher income compared to the neoadjuvant group (77.1% vs. 56.3%; p = 0.069). The two groups did not differ significantly by tumor grade, the neoadjuvant group is presented with a higher grade compared to adjuvant (90.3% vs. 68.6%; p = 0.079).
Table I - Baseline Characteristics of included UMMC Triple Negative Breast Cancer Patients (n= 67)

|                        | Neo Adjuvant (n=32) | Adjuvant Chemo (n = 35) | All Patients (n= 67) | p-Value |
|------------------------|---------------------|-------------------------|----------------------|---------|
| **Ethnicity**          |                     |                         |                      |         |
| Caucasians             | 4 (12.5%)           | 7 (20.0%)               | 11 (16.4%)           | 0.408   |
| African American       | 28 (87.5%)          | 28 (80.0%)              | 56 (83.6%)           |         |
| **Age**                |                     |                         |                      |         |
| ≤ 50 years             | 6 (18.8%)           | 7 (20.0%)               | 13 (19.4%)           | 0.963   |
| >50 - <60              | 12 (37.5%)          | 12 (34.3%)              | 24 (35.8%)           |         |
| > 60                   | 14 (43.8%)          | 16 (45.7%)              | 30 (44.8%)           |         |
| **BMI (kg/ m^2)**      |                     |                         |                      |         |
| Normal (18.5 - 24.9)   | 6 (18.8%)           | 3 (8.6%)                | 9 (13.4%)            | 0.521   |
| Overweight (25 - 29.9) | 10 (31.3%)          | 10 (28.6%)              | 20 (29.9%)           |         |
| Obese (30 - 39.9)      | 10 (31.3%)          | 16 (45.7%)              | 26 (38.8%)           |         |
| Morbidity (> 40)       | 6 (18.8%)           | 6 (17.1%)               | 12 (17.9%)           |         |
| **Income $**           |                     |                         |                      |         |
| ≤ $30,000              | 14 (43.8%)          | 8 (22.9%)               | 22 (32.8%)           | 0.069   |
| >$ 30,000              | 18 (56.3%)          | 27 (77.1%)              | 45 (67.2%)           |         |
| **Insurance**          |                     |                         |                      |         |
| Medicaid               | 11 (34.4%)          | 14 (40.0%)              | 25 (37.3%)           | 0.831   |
| Medicare               | 13 (40.6%)          | 12 (34.3%)              | 25 (37.3%)           |         |
| Private                | 5 (15.6%)           | 4 (11.4%)               | 9 (13.4%)            |         |
| Self-Pay               | 3 (9.4%)            | 5 (14.3%)               | 8 (11.9%)            |         |
| **Distance (Miles)**   |                     |                         |                      |         |
| ≤ 30 miles             | 15 (46.9%)          | 23 (65.7%)              | 38 (56.7%)           | 0.024   |
| 30-75 miles            | 15 (46.9%)          | 6 (17.1%)               | 21 (31.3%)           |         |
| > 75 miles             | 2 (6.3%)            | 6 (17.1%)               | 8 (11.9%)            |         |
| **Vital Status**       |                     |                         |                      |         |
| Alive                  | 22 (68.8%)          | 31 (88.6%)              | 53 (79.1%)           | 0.046   |
|                  | 10 (31.3%) | 4 (11.4%) | 14 (20.9%) |
|------------------|------------|-----------|------------|
| Dead             |            |           |            |

| Grade   | 0 (0.0%)  | 2 (5.7%)  | 2 (3.0%)  | 0.079   |
|---------|-----------|-----------|-----------|---------|
| I       |           |           |           |         |
| II      | 3 (9.7%)  | 9 (25.7%) | 12 (18.2%)|         |
| III     | 28 (90.3%)| 24 (68.6%)| 52 (78.8%)|         |

| 8th AJCC TNM stage | 1 (3.1%) | 17 (48.6%) | 18 (26.9%) | 0.000   |
|--------------------|----------|------------|------------|---------|
| Stage IIA          |          |            |            |         |
| Stage IIIB         |          |            |            |         |
| Stage IIIA         | 4 (12.5%)| 7 (20.0%)  | 11 (16.4%) |         |
| Stage IIIB         | 4 (12.5%)| 0 (0.0%)   | 4 (6.0%)   |         |
| Stage IIIC         | 23 (71.9%)| 9 (25.7%)  | 32 (47.8%) |         |

| Surgery             | 9 (28.1%) | 17 (48.6%) | 26 (38.8%) | 0.086   |
|---------------------|-----------|------------|------------|---------|
| Lumpectomy          |           |            |            |         |
| Mastectomy          | 23 (71.9%)| 18 (51.4%) | 41 (61.2%) |         |

| Lump Boost | 10 (31.3%) | 16 (45.7%) | 26 (38.8%) | 0.225   |
|------------|------------|------------|------------|---------|
| Yes        |            |            |            |         |
| No         | 22 (68.8%) | 19 (54.3%) | 41 (61.2%) |         |

| RT Type                        | 30 (93.8%) | 31 (88.6%) | 61 (91.0%) | 0.458   |
|--------------------------------|------------|------------|------------|---------|
| Conventional (50GY)            |            |            |            |         |
| Hypofraction (40.05Gy)         | 2 (6.3%)   | 4 (11.4%)  | 6 (9.0%)   |         |

| Local Recurrence | 5 (15.6%) | 3 (8.6%) | 8 (11.9%) | 0.374   |
|-------------------|----------|---------|----------|---------|
| Yes               |          |         |          |         |
| No                | 27 (84.4%)| 32 (91.4%)| 59 (88.1%)|         |

| Regional Recurrence | 0 (0.0%) | 2 (5.7%) | 2 (3.0%) | 0.17   |
|---------------------|----------|---------|----------|--------|
| Yes                 |          |         |          |        |
| No                  | 32 (100%)| 33 (94.3%)| 65 (97.0%)|        |
BMI= body mass index, AJCC = American Joint Committee on Cancer, n= Number, RT = Radiotherapy, UMMC = University of Mississippi Medical Center

The patients treated with adjuvant chemotherapy traveled less distance to the treatment facility compared to the patients treated with neoadjuvant chemotherapy (65.7% vs. 46.9%; p = 0.024). According to the 8th AJCC TNM staging system, more Stage IIIIC patients were treated with neoadjuvant chemotherapy compared to the patients treated with adjuvant chemotherapy (71.9% vs. 25.7%; p = 0.000). Stages IIA, IIB, IIIA, IIIB, and IIIIC accounting for 3.1%, 0%, 12.5%, 12.5% and 71.9% were treated with neoadjuvant chemotherapy while 48.6%, 5.7%, 20%, 0% and 25.7% were treated with adjuvant chemotherapy respectively, in 8th AJCC prognostic staging (p = 0.000). Distant metastasis occurred more in patients treated with neoadjuvant chemotherapy compared to the patients treated with adjuvant chemotherapy (34.4% vs. 8.6%; p = 0.009).

**Kaplan-Meier curves for Overall Survival, Local Control, and Disease-Free Survival**

Univariate analysis by Kaplan-Meier demonstrated that TNBC patients treated with adjuvant chemotherapy had better 5-year OS than those treated with neoadjuvant chemotherapy (92.2% vs. 65.1%; p = 0.002) at a median follow-up of 58 months (range 10 to 142 months) (shown in Fig. 2).

In terms of LC, the TNBC patients treated with adjuvant chemotherapy showed better 5-year LC rates compared to those treated with neoadjuvant chemotherapy (47.9% vs. 14.8%; p = 0.002) at a median follow-up of 47 months (range 1 to 135 months) (shown in Fig. 3).

In terms of DFS, TNBC patients treated with adjuvant chemotherapy showed better 5-year DFS rates compared to DFS estimated for TNBC patients treated with neoadjuvant chemotherapy 53.1% vs. 24.2%; p = 0.015) at a median follow-up of 47 months (range 1-135 months) (shown in Fig. 4).

**Cox Regression Analysis for Overall Survival**

The hazard ratios [HR] comparing treatment survival outcomes (neoadjuvant chemotherapy vs. adjuvant chemotherapy) about the risk of death was calculated by bivariante Cox regression (Table 2).

Regarding BMI, the TNBC patients treated with neoadjuvant chemotherapy showed a significant 45% decreased risk of mortality (HR 0.55, 95% CI, 0.30-1.00; p = 0.050) compared to patients treated with adjuvant chemotherapy.
The risk estimates for patients treated with neoadjuvant chemotherapy showed a statistically significant 94% decreased risk for death (HR 0.06, 95% CI, 0.00-0.73; p = 0.027) for distance traveled to the treatment facility. Followed by ten times the increased risk of patients with grade II (HR 10.75, 95% CI, 1.39–82.61; p = 0.022), and eight times significantly higher risk of death for stage IIIA (HR 8.52, 95% CI, 1.45–50.01; p = 0.018), compared to the patients treated with adjuvant chemotherapy.
### Table 2
**Bivariate Cox Regression Analysis**

| Neo-Adjuvant chemotherapy vs. Adjuvant chemotherapy | HR (95% CI) | P Value |
|---------------------------------------------------|-------------|---------|
| **Ethnicity**                                     | 0.43 (0.13–1.39) | 0.160   |
| **Age**                                           | 0.71 (0.37–1.37)  | 0.315   |
| **BMI (kg/m²)**                                   | 0.55 (0.30–1.00)  | **0.050**|
| **Income**                                        | 0.96 (0.31–2.94)  | 0.095   |
| **Insurance**                                     | 1.23 (0.74–2.05)  | 0.413   |
| **Distance (Miles)**                              |              |         |
| ≤ 30 miles                                        | 1            |         |
| 30–75 miles                                       | 0.06 (0.13–2.92) | 0.548   |
| > 75 miles                                        | 0.06 (0.00–0.73)  | **0.027**|
| **Tumor Grade**                                   |              |         |
| I                                                 | 1            |         |
| II                                                | 10.75 (1.39–82.61) | **0.022**|
| III                                               | 1.41 (0.30–6.58)  | 0.662   |
| **Surgery**                                       | 5.16 (0.65–40.86) | 0.120   |
| **RT type**                                       | 2.29 (0.48–10.91) | 0.296   |
| **8th AJCC TNM stage**                            |              |         |
| Stage IIA                                         | 1            |         |
| Stage IIB                                         | 1.38 (0.34–5.62)  | 0.645   |
| Stage IIIA                                        | 8.52 (1.45–50.01) | **0.018**|
| Stage IIIB                                        | 0.43 (0.78–2.44)  | 0.345   |
| Stage IIIC                                        | 0.35 (0.05–2.21)  | 0.269   |

BMI = body mass index, AJCC = American Joint Committee on Cancer, % = percentage, HR = Hazard Ratio, CI = Confident Interval

The multivariate Cox regression was built in which all the significant variables, BMI, distance traveled to the treatment facility, tumor grade, and 8th AJCC staging were added in the model (Table 3). The TNBC patients treated with neoadjuvant chemotherapy were twice the increased risk of death with morbid BMI compared to patients treated with adjuvant chemotherapy. The patients treated with neoadjuvant
chemotherapy who traveled long distances showed a 96% decreased risk of death, the tumor grade II showed 4 times increased risk and double the risk for stage IIIA. Stages IIIB and IIIC showed 81% and 87% decreased risk compared to TNBC patients treated with adjuvant chemotherapy. It is interesting to notice that none of the variables showed any statistical significance in the multivariate analyses.

Table 3
Multivariate Cox Regression Analysis

| Neo-Adjuvant chemotherapy vs. Adjuvant chemotherapy | HR (95% CI) | P Value |
|-----------------------------------------------------|-------------|---------|
| **BMI (kg/ m<sup>2</sup>)**                        |             |         |
| Normal (18.5–24.9)                                  | 1           |         |
| Overweight (25–29.9)                                 | 11.43 (0.96–135) | 0.054   |
| Obese (30–39.9)                                     | 7.37 (0.52-104.41) | 0.140   |
| Morbidity (> 40)                                    | 1.41 (0.14–14.03) | 0.768   |
| **Distance (Miles)**                                |             |         |
| ≤ 30 miles                                           | 1           |         |
| 30–75 miles                                          | 1.55 (0.13–17.69) | 0.724   |
| > 75 miles                                           | 0.04 (0.00-1.76) | 0.097   |
| **Tumor Grade**                                     |             |         |
| I                                                    | 1           |         |
| II                                                   | 4.62 (0.22–95.52) | 0.322   |
| III                                                  | 1.48 (0.11–20.05) | 0.766   |
| **8th AJCC TNM stage**                              |             |         |
| Stage IIA                                            | 1           |         |
| Stage IIB                                            |             |         |
| Stage IIIA                                           | 1.07 (0.11–10.4) | 0.947   |
| Stage IIIB                                           | 0.19 (0.01–2.36) | 0.198   |
| Stage IIIC                                           | 0.13 (0.00-5.04) | 0.274   |

BMI = body mass index, AJCC = American Joint Committee on Cancer, % = percentage, HR = Hazard Ratio, CI = Confident Interval
Discussion

In the National Surgical Breast and Bowel Project (NSABP) Trial B-17 at 15 years, the radiation showed a lower rate of ipsilateral invasive recurrence 8.9 versus 19.4 percent, when compared with excision alone [13]. The findings were reported from a large observational study of the Surveillance, Epidemiology, and End Results (SEER) database that included over 100,000 patients; the subgroup of 60,000 women was treated with breast conservation therapy (BCT) with or without radiation being compared with lumpectomy alone. The radiation treatment was associated at 10 years with a lower rate of ipsilateral breast cancer recurrence 2.5 versus 4.9 percent in the lumpectomy. The whole-breast radiotherapy (WBRT) was delivered to the entire breast in 1.8 to 2 Gy daily fractions over 4.5 to 5 weeks to a total dose of 45 to 50 Gy. The women with adjuvant radiation as a component of BCT with an observational study in 1323 women with a median follow-up of 6.6 years suggested that earlier initiation of radiation in ≤ 8 weeks) was associated with a lower incidence of ipsilateral breast tumor recurrence. In two single-institution trials that enrolled a total of 145 women who had undergone breast-conserving surgery for malignancy, patients received accelerated radiation with 41 to 42 Gy delivered over 15 to 16 fractions. In a combined analysis, the recurrence rate at five years was 4 percent, which was similar to the rate of recurrence following WBRT reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial [13]. Several large, prospective, randomized trials are nearing target accrual or have been completed, including the NSABP/RTOG trial [14], the Milan-based intraoperative radiation trial [15], and the international TARGIT trial [16], and the status of each is discussed. The American Society for Radiation Oncology has also published a consensus statement to guide the use of PBI until randomized, non-inferiority trial done at 97 hospitals [17].

The Danish Breast Cancer Cooperative Group (DBCG) 82 b and c trials have limited addressed the question of whether postmastectomy radiation to the axillary, supra/infrACLavicular, and ipsilateral internal mammary nodes improved breast cancer outcomes in pre-and postmenopausal patients, respectively [18, 19]. These studies included node-positive, as well as high-risk, node-negative diseases, which were defined as tumors that were > four to five cm or invaded the skin or fascia. This demonstrated improved disease-free and overall survival associated with radiation among women treated with RT after mastectomy.

It should be noted that the number of patients with node-negative disease was small in the studies with approximately 130 women in each Danish study. The limited data for postmastectomy radiation in triple-negative disease suggest a treatment benefit. The treatment was given to women with triple-negative breast cancer who lack other high-risk features. In a randomized trial of patients with triple-negative breast cancer treated with mastectomy and adjuvant chemotherapy with or without postmastectomy RT, at a median follow-up of 86 months, women who received postmastectomy chest wall RT had significantly better five-year relapse-free survival 88 versus 75 percent and overall survival 90 versus 79 percent when compared with those who received chemotherapy alone [20]. The relapse can occur within two years of primary treatment and distant metastatic disease is already present in 25 to 30 percent of cases. There is 15 to 40 percent of recurrences involve the chest wall and axillary or supraclavicular
lymph nodes, breast cancer has the potential to metastasize to almost every organ in the body. The most common sites of metastases are bone, liver, and lung. Approximately 50 to 75 percent of patients who relapse distantly do so in a single organ; the remainder will develop diffuse metastatic disease. Less than 5 percent of patients will manifest central nervous system involvement as the first site of metastatic disease [21].

Given that the prognosis of small, node-negative, triple-negative breast cancers (TNBCs) is generally favorable, the benefit of adjuvant chemotherapy is unclear. In a retrospective review of almost 4400 patients with node-negative pathologic T1 TNBCs, adjuvant chemotherapy was administered in 53 percent of cases [22]. In multivariate analysis, adjuvant chemotherapy improved breast cancer-specific survival in the overall group, but not for patients with T1a tumors, although there were only 18 patients in this subset. We administer adjuvant chemotherapy for patients with node-negative tumors that are ≥ T1b, but typically not for node-negative, T1a TNBCs, although some such patients may reasonably elect for chemotherapy, given limitations in available data.

Neoadjuvant chemotherapy is associated with high rates of clinical response and a greater likelihood of facilitating cosmetically acceptable surgery. Outcomes for patients receiving neoadjuvant versus adjuvant chemotherapy were demonstrated in an individual patient data meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group, which was based on data from 4756 women in 10 trials initiated between 1983 and 2002 [23, 24]. The 15-year local recurrence in patients treated with neoadjuvant chemotherapy (21.4% vs. 15.9%; p = 0.0001) compared to adjuvant chemotherapy. No significant difference between the two groups was noted for distant recurrence (38.2% vs. 38.0%; p = 0.45).

Our institution data reveal the control and survival rates for triple negative breast cancers treated by conventional or hypo fraction radiation with neo-adjuvant or adjuvant chemotherapy. In our cohort, balanced arms show that adjuvant chemotherapy is better in clinical outcomes than neoadjuvant chemotherapy. The patients receiving adjunctive chemotherapy had a better 5-year LC, DFS and OS compared to neoadjuvant chemotherapy. The overall rates of neoadjuvant chemotherapy vs. adjuvant chemotherapy are, LC 14.8% vs. 47.9 % (p = 0.002), DFS 24.2% vs. 53.1% (p = 0.015) and OS 65.1% vs. 92.2% (p = 0.002).

It could be hypothesized that the differences in outcomes can be purely due to the more advanced loco-regional disease stage of the neoadjuvant cohort. Yet, in the multivariate analyses, the stage was not a significant factor. Only additional patients and/ or studies from other institutions – prospective or retrospective - can help resolve this contradiction.

**Summary And Conclusion**

Our study shows a clear benefit for triple negative breast cancers treated by radiation and adjuvant chemotherapy compared to radiation and neoadjuvant chemotherapy in our cohort of triple negative node-negative breast cancer patients in the local control, DFS and OS. Given the limited number of
patients in our cohort, we caution that our findings be considered hypothesis-generating than practice-changing until additional data become available.

**Abbreviations**

AJCC American Joint Committee on Cancer

BCT Breast Conservation Therapy

BMI Body Mass Index

BRCA Breast Cancer Gene

CI Confident Interval

DBCG Danish Breast Cancer Cooperative Group

DFS Disease-Free Survival

ER Estrogen Receptor

HER2 Human Epidermal Growth Factor Receptor 2

HR Hazard Ratio

LC Local Control

M Distant Metastasis

N Adjacent Nodes

NSABP National Surgical Breast and Bowel Project

OS Overall Survival

pCR Pathological Complete Response

PR Progesterone Receptor

REDCap Research Electronic Data Capture

RT Radiotherapy

SEER Surveillance, Epidemiology, and End Results

T Primary Tumor
TNBC Triple Negative Breast Cancer

UMMC University of Mississippi Medical Center

WBRT Whole-Breast Radiotherapy

Declarations

**Ethics approval and consent to participate:** The subjects (or their parents or guardians) written consent was waived by Health Insurance Portability and Accountability Act (HIPPA) due to the retrospective nature of the study and patient identifiers were removed before extracting the data. This study is approved by the University of Mississippi Medical Center Institutional Review Board (IRB) protocol #2018-0218

**Consent for Publication:** Not applicable

**Availability of data and Materials:** This study does not contain any sequence/ expression data, protein/molecule characterizations, annotations, and taxonomy data to be deposited in a public repository. Patient identifiers were removed before extracting data and will be shared upon reasonable request to Dr. Mary R Nittala or senior author Dr. Srinivasan Vijayakumar.

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Figures
Breast Cancer Patients treated at UMMC from 2007 to 2017
(n = 376)

Exclude (n= 304)
  • Ductal carcinoma in situ (n = 45)
  • Paget’s (n=2)
  • Tumor status unknown (n=17)
  • ER+ PR+ HER2 + (n=24)
  • ER + PR + HER2- (n=134)
  • ER + PR - HER2 + (n=15)
  • ER + PR - HER2 - (n=36)
  • ER - PR+ HER2 + (n=3)
  • ER- PR-HER2+ (n=23)
  • ER- PR + HER2 - (n=5)

Include:
Triple Negative Breast Cancer patients; ER-, PR-, HER2- (n= 72)

Exclude (n=5)
Triple Negative Breast Cancer patients except Caucasians and African Americans

Final Selection: (n= 67)
  • T1N0M0 (n= 16)
  • T1N1M0 (N=3)
  • T2N0M0 (n=10)
  • T2N1M0(N=13)
  • T2N2/N3M0 (N=5)
  • ALL T3 (N=7)
  • ALL T4 (N=13)

Neoadjuvant Chemo: (n= 32)
  • T1N0M0 (n= 0)
  • T1N1M0 (n=1)
  • T2N0M0 (n=4)
  • T2N1M0(n=9)
  • T2N2/N3M0 (n=4)
  • ALL T3 (n=4)
  • ALL T4 (n=10)

Adjuvant Chemo: (n= 35)
  • T1N0M0 (n= 16)
  • T1N1M0 (n=2)
  • T2N0M0 (n=5)
  • T2N1M0(n=4)
  • T2N2/N3M0 (n=1)
  • ALL T3 (n=3)
  • ALL T4 (n=3)

Figure 1
Flow chart for Triple Negative Breast Cancer Patients Cohort selection. UMMC, University of Mississippi Medical Center; ER, estrogen receptor; PR, progesterone receptor, HER2, human epidermal growth factor receptor 2; n, number; %, percentage.
Figure 2

Overall Survival of UMMC Triple Negative Breast Cancer Patients (n= 67). UMMC, University of Mississippi Medical Center; n, number.
Figure 3

Local Control of UMMC Triple Negative Breast Cancer Patients (n= 67) UMMC, University of Mississippi Medical Center; n, number.
Figure 4

Disease Free Survival of UMMC Triple Negative Breast Cancer Patients (n= 67) UMMC, University of Mississippi Medical Center; n, number.