A Retrospective Cohort Study on the Disease-Free Survival and Overall Survival of Patients with Stage I-III Triple-Negative Breast Cancer given Adjuvant Chemotherapy in the Makati Medical Center

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Abstract

Background. Triple-negative breast cancer (TNBC) comprises 15-20% of all breast cancers and is marked by early relapse and poor overall survival. Adjuvant chemotherapy has become the standard of care for these patients albeit to this time there is no consensus on its optimal chemotherapy regimen. This study determined the disease-free-survival (DFS) and overall survival (OS) of patients with stage I-III triple-negative breast cancer given adjuvant chemotherapy in Makati Medical Center from 2000 to 2015.

Methods. A single institution (Makati Medical Center), retrospective cohort was conducted involving 157 stage I-III triple-negative breast cancer patients, diagnosed from January 2000 to June 2015, who completed an adjuvant chemotherapy regimen and had at least 3 years of follow up with their medical oncologist. Review of charts of these patients was done, and the demographic, clinical, histopathologic, chemotherapy, recurrence and mortality data were collected and analyzed. The OS and DFS rates were estimated using the Kaplan-Meier method.

Results. 107 stage I-III triple-negative breast cancer patients who met eligibility criteria were included in the analysis. The most common chemotherapy regimens were sequential anthracycline-taxane (32 patients, 29.09%) and anthracycline-based regimens (32 patients, 29.09%). The 5-year median OS of TNBC patients given adjuvant chemotherapy was 78.94% (95% CI: 69% to 86%) while the 5-year median DFS of TNBC patients was 71.71% (95% CI: 61.68% – 79.5%). There was no significant association between overall survival or disease-free survival and treatment with a particular chemotherapy regimen.

Conclusions. Adjuvant chemotherapy with sequential anthracycline-taxane, concurrent anthracycline-taxane, CMF, anthracycline-based and taxane-based regimens among stage I-III triple-negative breast cancer patients in Makati Medical Center resulted in comparable overall survival and disease-free survival. The use of immune checkpoint inhibitors presents a viable option in TNBC as demonstrated in the Impassion 130 and KEYNOTE 119 trials, and should be further evaluated in the Philippine setting.

Keywords: triple-negative breast cancer, adjuvant chemotherapy, overall survival, disease free survival

Introduction

Among Philippine women, breast cancer is the most common cancer and the leading cause of cancer-related mortality, with an estimated 20,267 cases and 7384 mortalities diagnosed each year[1]. While other types of breast cancer have clearly defined treatment options, disagreement and uncertainty remain with regards to the ideal treatment regimen for patients with triple-negative breast cancer (TNBC), which is characterized by the absence of estrogen receptor, progesterone receptor expression and lack of human epidermal growth factor receptor 2/neuprotooncogene (HER-2/neu) over-expression[2].

TNBC comprise 15-20% of breast cancers and is marked by poor survival outcomes. In the Philippines, TNBC is less common, comprising only 8.9% of diagnosed breast cancer patients. [3] Five-year overall survival for patients with TNBC was considerably worse at 77% compared to other breast cancer types (93% five-year OFS). [4] Relapse rate is high during the first 3-5 years after surgery, with subsequent decline in recurrence risk thereafter. [5, 6] Among patients with early-stage breast cancer, TNBC was an independent predictor of distant metastasis and decreased disease-free survival and death. [7-8]

In current clinical practice, chemotherapy is advocated for patients with TNBC. These tumors show improved pathologic complete response (30-40%) with adjuvant chemotherapy compared to non-triple negative breast cancers[9]. Available chemotherapy options include cyclophosphamide-methotrexate-5-fluorouracil (CMF), anthracycline or taxane-based regimens[10]. Recent studies demonstrated that concurrent anthracycline-taxane regimen had better disease-free survival and overall survival compared to anthracycline-based or taxane-based regimen alone[11]. Promisingly, Swain et al (2010) determined that sequential

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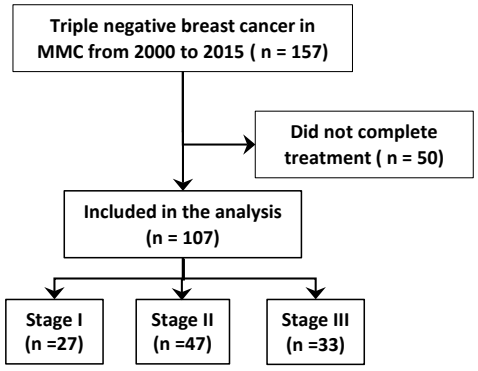

Figure 1. Flow Diagram of Patient Evaluation

anthracyline-taxane chemotherapy provided a significant increase in disease-free survival vis-à-vis concurrent regimen[12].

Despite the variety of available chemotherapy regimens, there is no consensus on the optimal regimen that would improve survival outcomes for TNBC patients. According to the Philippine Society of Medical Oncology, there is no published data on the survival outcomes of TNBC in the Philippines.

Objectives

Primary Objective: To determine the 3-year and 5-year overall survival and disease-free survival rates of stage I-III TNBC patients given adjuvant chemotherapy in Makati Medical Center.

Secondary Objectives

1. To describe the clinical characteristics of TNBC patients
2. To identify prognostic factors that signify poor outcomes for TNBC patients

Methods

The flow diagram of patient evaluation is depicted in Figure 1. A single institution (Makati Medical Center) retrospective cohort was conducted involving 157 stage I-III TNBC private patients who were given adjuvant chemotherapy from January 2000 to June 2015. 50 patients were lost to follow up, resulting in a final cohort of 107 patients. Upon inquiry, patients were lost to follow up due to financial constraints, chemotherapy-related adverse drug effects, or desire to try alternative treatment.

The study used a purposive sample, comprising all stage I-III TNBC private patients diagnosed in Makati Medical Center who completed a chemotherapy regimen. either in the inpatient or outpatient department, and had regular follow up with their medical oncologist for at least 3 years or until the patient expired. The minimum follow-up of three years was strictly followed, unless the patient expired prior to this time point. Patients were followed up as per the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines[14]. Additional inclusion criteria comprised provision of surgery and/or radiotherapy in accord with local tumor guidelines, and definite histopathologic diagnosis of TNBC. Patients who had incomplete data, an active infection, another primary malignancy, uncontrolled systemic illnesses or distant metastasis on initial presentation were excluded.

Table I. Clinical Data of TNBC Patients Gathered

Patient age at diagnosis	Date of last follow up
Stage of breast cancer upon diagnosis (TNM classification)	Cause of mortality and time point of death
Laterality of breast cancer	Comorbid conditions
Chemotherapy regimen received with number of cycles	Surgery type, Surgical margins
Adverse drug effects from chemotherapy	Histologic type
Whether radiotherapy was given	Tumor size, tumor grade, Lymph node status, and presence of lymphovascular invasion
Development of local/distant recurrence or second primary	ER/PR/HER2neu status

Table II. Chemotherapy Regimen Employed in Makati Medical Center

Chemotherapy regimen	Standard dose
Concurrent anthracycline / taxane	• Doxorubicin 60 mg/m^2 with docetaxel 80 mg/m^2 for 6 cycles • Doxorubicin 60 mg/m^2, docetaxel 75 mg/m^2 and cyclophosphamide 500 mg/m^2 for 6 cycles
Taxane-based	• Docetaxel 75 mg/m^2 with cyclophosphamide 600 mg/m^2 for 6 cycles
Cyclophosphamide, methotrexate, 5-fluorouracil	• Cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 for 6 cycles
Sequential anthracycline - taxane	• Doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2 for 4 cycles followed by docetaxel 100 mg/m^2 or paclitaxel 80 mg/m^2 for 4 cycles • 5-fluorouracil 500 mg/m^2, epirubicin100 mg/m^2, cyclophosphamide 500 mg/m^2 (FEC) combination for 3 cycles followed by docetaxel 100 mg/m^2 for 3 cycles
Anthracycline-based	• 5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2 / epirubicin 80 mg/m^2, cyclophosphamide 500 mg/m^2 (FAC/FEC) combination for 6 cycles • Doxorubicin 60 mg/m^2 with cyclophosphamide 600 mg/m^2 for 6 cycles

Data was gathered from patient records of the medical oncologists (see Table I). Personal information of the patients was not collected in accord with the Data Privacy Act of 2012[15]. The institutional review board of the Makati Medical Center approved this study.

TNBC was defined by negative estrogen receptor and progresterone receptor expression and lack of human epidermal growth factor-2 overexpression. To standardize the evaluation of breast biomarkers, the

pathologists employed the standards espoused by the American Joint Committee on Cancer Staging Manual, 8th edition[13]. Makati Medical Center employed at least two independent breast pathologists to validate histopathologic results to minimize risk for discordance.

There were a variety of chemotherapy regimens employed by medical oncologists in Makati Medical Center as adjuvant therapy for TNBC patients (see Table II). Patients who underwent neoadjuvant chemotherapy were not included.

Survival outcomes were assessed via disease-free survival and overall survival. Disease-free survival was defined as the time from histopathologic diagnosis of breast cancer to first local or distant recurrence, development of second primary or death from any cause. Overall survival was defined as the time from histopathologic diagnosis of breast cancer to death from any cause. Patients without recurrence or death were censored at the time of last follow up with their medical oncologist.

Local recurrence was defined as clinically and histologically documented relapse in the ipsilateral breast or chest wall and/or regional nodes. Distant recurrence was defined as clinical evidence of distant disease based on clinical and/or imaging findings. A second primary was defined as clinically and histologically documented evidence of another malignancy not related to the primary tumor. RECIST 1.1 was utilized to confirm disease progression.

Sample Size. The primary aim of this study was to determine the 3-year and 5-year overall survival and disease-free survival rates of patients with TNBC given adjuvant chemotherapy and it was used as the basis for the calculation of sample size. The sample size was computed using an online software, OpenEpi, Version 3. Liedtke et al. (2008) determined that the 3-year disease-free survival of patients with TNBC given adjuvant chemotherapy was 63%[9]. The margin of error used was 10%. At a 95% confidence interval and accounting for 10% attrition rate, the computed sample size was 100 patients.

Simple Regression and Multivariate Analysis. Descriptive statistics were used to summarize the clinical characteristics of participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Kaplan-Meier analysis was applied to estimate cumulative survival probabilities and median survival time, while the log-rank test was used to determine whether differences in survival probability were significant between groups. Multivariate analysis was done via Cox proportional hazards regression by the backward stepwise approach. Crude and adjusted hazard ratios were presented with 95% confidence intervals and p-values.

All valid data were included in the analysis. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Ethical Considerations. All personal information of the patients were not collected in accord with the Data Privacy Act of 2012[15]. The level of risk was minimal because the personal information of the patients was not collected to maintain patient confidentiality.

Results

Demographic, clinical characteristics and treatment regimens of the cohort were shown in Table III. The average age of the cohort was 50.2 ± 10.8 years (median age: 49 years, range: 28-79 years). Patients were followed up for a median of 54 months (range: 5-210 months).

In terms of histologic picture, the most common type of breast cancer was invasive ductal carcinoma (95.33%).

Majority of patients had tumor size between 2 to 5 cm (47.66%), histologic grade 3 (60.75%), no lymphovascular invasion (72.9%), and no lymph node involvement (60.75%). Stage 2 disease was most prevalent, diagnosed in 43.93% of the cohort.

The preferred adjuvant chemotherapy regimens include sequential anthracycline-taxane (29.91%) and anthracycline-based chemotherapy (29.91%). Sequential anthracycline-taxane chemotherapy was employed more frequently among patients with stage II or stage III disease (34.04% of stage II patients and 45.45% of stage III patients, respectively). On the other hand, anthracycline-based chemotherapy was more commonly used in patients with stage I or II disease (44.44% of stage I patients, 36.17% of stage II patients, respectively). The most common adverse drug effects experienced by patients given adjuvant chemotherapy was nausea and vomiting (50.91%).

Among the study participants, 41.12% developed disease recurrence, majority of which were distant metastasis, seen in 22.43% of patients in this cohort. The most common sites for distant metastasis (N = 24) were the lungs (37.5% of distant recurrence) and bone (333.33%). Local recurrence (N = 10) occurred most frequently via chest wall metastasis (40% of local recurrence), followed by involvement of the ipsilateral breast (18.18% of local recurrence). Ten patients developed a second primary malignancy, with the most common site being the contralateral breast (70%). There were 27 recorded deaths in the study (25.23%), with the leading cause of death being respiratory failure (62.96% of deaths) (see Table III).

The estimated 3-year and 5-year overall survival rates were 85.23% (95% CI 77%—91%) and 78.94% (95% CI 69%—86%), respectively (see Table IV). The 3-year and 5-year overall survival rates for those with stage 3 cancer were 69.21% and 61.92%, respectively; in contrast, 3-year and 5-year overall survival rates for stage 2 patients were 89.26% and 79.78%. All stage 1 patients were alive at the 5-year mark.

The estimated 3-year and 5-year disease-free survival rates were 77.93% (95 CI 68.9% - 84.62%) and 71.71% (95% CI 61.68% - 79.55%), respectively (see Table IV). For patients with stage 3 disease, the 3-year and 5-year disease-free survival rates were lower at 60.89% and 53.25%, compared to those with stage 2 disease where

Table III. Demographic, clinical characteristics and treatment regimen of patients (n=107)

Parameters	Frequency (%); Mean ± SD			
	Total (n=107)	Stage I (n=27)	Stage II (n=47)	Stage III (n=33)
Age (years)	50.2 ± 10.8	49.3 ± 11.2	49.7 ± 10.3	51.4 ± 11.3
Tumor laterality				
Left	58 (54.21)	16 (59.26)	24 (51.06)	18 (54.55)
Right	49 (45.79)	11 (40.74)	23 (48.94)	15 (45.45)
Comorbidities				
Hypertension	40 (37.38)	8 (29.63)	17 (36.17)	15 (45.45)
Dyslipidemia	4 (3.74)	1 (3.70)	1 (2.13)	2 (6.06)
Diabetes mellitus type 2	4 (3.74)	2 (7.41)	2 (2.78)	0
Asthma	2 (1.87)	0	1 (2.13)	1(3.03)
COPD	1 (3.03)	1 (3.70)	0	0
Size of breast cancer (cm)				
≤ 2	38 (35.51)	24 (88.89)	5 (10.64)	9 (27.27)
> 2 to < 5	51 (47.66)	3 (11.11)	40 (85.11)	8 (24.24)
≥ 5	12 (11.21)	0	2 (4.26)	10 (30.30)
Growing into chest wall or skin	6 (5.61)	0	0	6 (18.18)
Histologic type				
Invasive ductal	102 (95.33)	26 (96.30)	43 (91.49)	33 (100)
Invasive lobular	2 (1.87)	1 (3.70)	1 (2.13)	0
Mucinous	1 (0.93)	0	1 (2.13)	0
Invasive papillary	1 (0.93)	0	1 (2.13)	0
Metaplastic carcinoma	1 (0.93)	0	1 (2.13)	0
Histopathologic grade				
1	4 (3.74)	2 (7.41)	1 (2.13)	1 (3.03)
2	38 (35.51)	13 (48.15)	21 (44.68)	4 (12.12)
3	65 (60.75)	12 (44.44)	25 (53.19)	28 (84.85)
Lymphovascular invasion	29 (27.10)	2 (7.41)	12 (25.53)	15 (45.45)
Lymph nodes	Total	Stage 1	Stage 2	Stage 3
None	65 (60.75)	27 (100)	29 (61.70)	9 (27.27)
1 – 3	19 (17.76)	0	13 (27.66)	6 (18.18)
4 – 9	8 (7.48)	0	1 (2.13)	7 (21.21)
≥10	17 (14.02)	0	4 (8.51)	11 (33.33)
Surgical management				
MRM	91 (85.05)	18 (66.67)	44 (93.62)	29 (87.88)
Lumpectomy	16 (14.95)	9 (33.33)	3 (6.38)	4 (12.12)
Positive surgical margins	1 (0.93)	0	0	1 (3.03)
Chemotherapy regimen				
Concurrent anthracycline-taxane	15 (14.02)	1 (3.70)	7 (14.89)	7 (21.21)
Doxorubicin + Docetaxel for 6 cycles	5 (33.33)	1 (100)	3 (42.86)	1 (14.29)
Doxorubicin + Docetaxel + Cyclophosphamide (TAC) for 6 cycles	10 (66.67)	0	4 (57.14)	6 (85.71)
Taxane – based chemotherapy (Docetaxel + Cyclophosphamide for 6 cycles)	20 (18.69)	9 (33.33)	6 (12.77)	5 (15.15)
CMF	8 (7.48)	4 (14.81)	1 (2.13)	3 (9.09)
Sequential anthracycline-taxane	32 (29.91)	1 (3.70)	16 (34.04)	15 (45.45)
Doxorubicin + Cyclophosphamide for 4 cycles then Docetaxel/ paclitaxel for 4 cycles	30 (93.75)	1 (100)	15 (93.75)	14 (93.33)
5-fluorouracil + Epirubicin + Cyclophosphamide (FEC) for 3 cycles then docetaxel for 3 cycles	2 (6.25)	0	1 (6.25)	1 (6.67)
Anthracycline-based chemotherapy	32 (29.91)	12 (44.44)	17 (36.17)	3 (9.09)
5-fluorouracil + Doxorubicin/ epirubicin + Cyclophosphamide (FAC /FEC) for 6 Cycles	21 (65.63)	8 (66.67)	12 (70.59)	1 (33.33)
Doxorubicin + Cyclophosphamide for 6 Cycles	11 (34.38)	4 (33.33)	5 (29.41)	2 (66.67)
Radiotherapy	60 (56.07)	12 (44.44)	20 (42.55)	28 (84.85)
Median number of months of follow up	54 months	5 to 210		
Adverse drug effects	Total	Stage 1	Stage 2	Stage 3
Nausea or vomiting	55 (51.40)	12 (44.44)	27 (57.45)	16 (48.49)
Generalized body weakness	26 (24.30)	8 (29.63)	9 (19.15)	9 (27.27)
Neutropenia	13 (12.15)	3 (11.11)	5 (10.64)	5 (15.15)
Diarrhea	1 (0.93)	0	1 (2.13)	0
Rashes	1 (0.93)	0	0	1 (3.03)
None	11 (10.28)	4 (14.81)	5 (10.64)	2 (6.06)

FU, fluorouracil; CMF, cyclophosphamide + methotrexate + fluorouracil; COPD, chronic obstructive pulmonary disease.; FAC, 5-fluorouracil, + adriamycin + cyclophosphamide; FEC, 5-fluorouracil + epirubicin + cyclophosphamide, MRM, modified radical mastectomy.

3-year and 5-year disease-free survival were 80.77% and 74.27%. Disease-free survival was highest for stage 1 patients, with 3-year disease survival of 96.15% and 5-year disease-free survival of 91.88%.

Table IV. Recurrence and mortality in women with TNBC who underwent adjuvant chemotherapy

	Total (N = 107)	Stage I (N = 27)	Stage II (N = 47)	Stage III (N = 33)
Local	10 (10)	1 (3.70)	2 (4.26)	7 (21.21)
Chest wall metastasis	4 (40)	0	2 (100)	2 (28.57)
Ipsilateral breast	2 (20)	0	0	2 (28.57)
Left axillary LN	1 (10)	0	0	1 (14.29)
Left supraclavicular LN	1 (10)	0	0	1 (14.29)
Right supraclavicular LN	1 (10)	1 (100)	0	0
Supraclavicular and mediastinal LN	1 (10)	0	0	1 (14.29)
Distant	24 (22.43)	1 (3.70)	11 (23.40)	12 (36.36)
Bone	8 (29.17)	1 (100)	3 (27.27)	3 (25)
Brain	4 (12.5)	0	0	3 (25)
Liver	4 (12.5)	0	2 (18.18)	1 (8.33)
Lungs	10 (33.33)	0	4 (36.36)	4 (33.33)
Lungs and brain	1 (4.17)	0	1 (9.09)	0
Lungs and liver	1 (4.17)	0	1 (9.09)	0
Pleura	1 (4.17)	0	0	1 (8.33)
Second primary	10 (9.09)	4 (14.81)	3 (6.38)	3 (8.33)
Contralateral breast	7 (70)	3 (75)	1 (33.33)	3 (100)
Esophageal	1 (10)	1 (25)	0	0
Papillary thyroid	1 (10)	0	1 (33.33)	0
Spindle cell tumor of the brain	1 (10)	0	1 (33.33)	0
Death (n=27)				
Respiratory failure	17 (62.96)			
Infection	7 (25.93)			
Liver failure	3 (11.11)			

Table V. Survival estimates and recurrence data

	Survival Rate	Confidence Interval
Overall survival		
3 – year survival	85.23%	77% to 91%
5 – year survival	78.94%	69% to 86%
Stage 1		
3 – year survival	100	-
5 – year survival	100	-
Stage 2		
3 – year survival	89.26%	76% to 95%
5 – year survival	79.78%	63% to 90%
Stage 3		
3 – year survival	69.21%	51% to 82%
5 – year survival	61.92%	43% to 76%
Disease-free survival		
3 – year survival	77.93%	68.90% to 84.62%
5 – year survival	71.71%	61.68% to 79.55%
Stage 1		
3 – year survival	96.15%	75.69% to 99.45%
5 – year survival	91.88%	71.18% to 97.91%
Stage 2		
3 – year survival	80.77%	66.30% to 89.50%
5 – year survival	74.27%	57.65% to 85.16%
Stage 3		
3 – year survival	60.89%	43.06% to 74.67%
5 – year survival	53.25%	34.92% to 68.56%
Median disease-free survival	142 months	
Median time to disease recurrence	67 months	59 to 81
Median interval from disease recurrence to mortality	8 months	3 to 13

Median disease-free survival time was estimated to be 142 months. The median time to develop disease recurrence was 67 months (range: 59 to 81 months), while the median interval from disease recurrence to mortality was 8 months (range: 3 to 13 months).

A 75% cumulative overall survival was seen approximately 62 months post-diagnosis (Figure 2). The risk of death was increased in the first 5 years after diagnosis, as evidenced by the relatively steeper curve seen in the first 62 months, with subsequent decline in the risk of death over time, as evidenced by the flatter curve after 62 months.

On simple regression, only stage III disease appeared to predict mortality (crude Hazard Ratio 3.00, 95% CI 1.19 – 7.57) (see Table V). After controlling for other patient factors, the multivariate statistical analysis revealed that the histopathologic grade was the only significant variable influencing overall survival. Patients with grade 3 tumor had a risk equivalent of more than 3.5-fold (adjusted Hazard Ratio 3.591, 95% CI 1.5-8.09) that of grade 1 cancer.

Overall survival estimates were correspondingly worse with a higher stage of disease (Figure 3). For the overall survival curve disaggregated by stage, the log-rank statistic was 15.70, with a p-value <0.0004. The overall survival curves of TNBC patients were significantly different with respect to the stage of breast cancer at a 0.05 level of significance. Survival curves disaggregated according to the chemotherapeutic regimen were depicted in Figure 4. The log-rank statistic was 2.55, with a p-value of 0.636, indicative that overall survival curves of TNBC patients were not significantly different with respect to chemotherapy regimen.

Three-fourths of patients remained disease-free at approximately 39 months. The median disease-free survival time was pegged at 142 months (Figure 5). Kaplan-Meier curves disaggregated by cancer stage and chemotherapeutic regimen are depicted in Figures 6 and 7, respectively. For the disease-free survival curve disaggregated by

Table VI. Cox proportional hazards regression

	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*p*
Age	1.009 (0.98 – 1.04)	0.56		
Cancer stage				
I	(reference)			
II	1.76 (0.67 – 4.60)	0.25		
III	3.00 (1.19 – 7.57)	**0.02**		
Histologic diagnosis				
Invasive ductal	(reference)			
Invasive lobular	$1.57e^{-16}$	-		
Mucinous adenocarcinoma	1.55 (0.21 – 11.53)	0.67		
Invasive papillary	3.27 (0.44 – 24.09)	0.24		
Metaplastic carcinoma	$1.54e^{-16}$	-		
Histopathologic grade				
1	(reference)			
2	0.40 (0.08 – 2.06)	0.28	3.59	
3	1.80 (0.41 – 7.97)	0.44	(1.59 – 8.09)	**0.002**
Surgical management				
MRM	(reference)			
Lumpectomy	0.55 (0.17 – 1.79)	0.32		
Chemotherapy regimen				
Sequential anthracycline-taxane	0.75 (0.27 – 2.09)	0.58		
Anthracycline-based	0.82 (0.31 – 2.20)	0.69		
Taxane-based	0.80 (0.27 – 2.40)	0.70		
Concurrent anthracycline-taxane	(reference)			
CMF	0.23 (0.03 – 1.92)	0.17		
Radiotherapy	1.75 (0.90 – 3.39)	0.10		

stage, the log-rank statistic was 6.48, with a p-value of 0.0391. The disease-free survival curves of TNBC patients were significantly different with respect to the stage of breast cancer. On the other hand, for the disease-free survival curve disaggregated by chemotherapy regimen, the log-rank statistic was 2.15, with a p-value of 0.708, indicative that the disease-free survival curves of TNBC patients were not significantly different with respect to chemotherapy regimen.

Discussion

Adjuvant chemotherapy is the primary therapeutic option for patients with TNBC. Given the dearth of Philippine data on survival outcomes of TNBC, this study provides the first local data on the overall survival and disease-free survival of patients with TNBC given adjuvant chemotherapy.

The estimated 5-year overall survival (OS) and disease-free survival (DFS) of patients with TNBC given adjuvant chemotherapy in Makati Medical Center were 78.94% and 71.71%, respectively. The estimated 5-year OS of TNBC patients in Makati Medical Center was higher compared to the 5-year estimated OS rate of 66.5% seen in the study conducted by Steponaviciene et al (2011), which studied 99 TNBC from Poland[16]. A possible explanation for the higher survival rate in the present study was that all patients were given adjuvant chemotherapy while the study of Steponaviciene had 26.3% of patients who were not given adjuvant chemotherapy[16]. This suggests the possibility of improved survival rates for TNBC patients given adjuvant chemotherapy. The present study also had a younger cohort, with a median age of 49 years, while the Polish study had a cohort with a median age of 55 years. Further study is needed in the local setting to

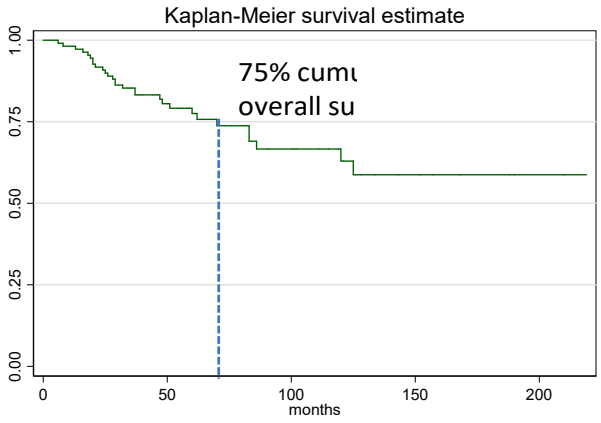

Figure 2. Overall Survivial Curve for all Patients

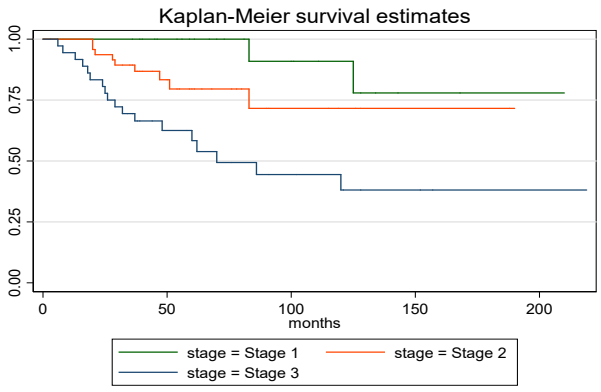

Figure 3. Overall Survival Curve Disaggregated by Stage

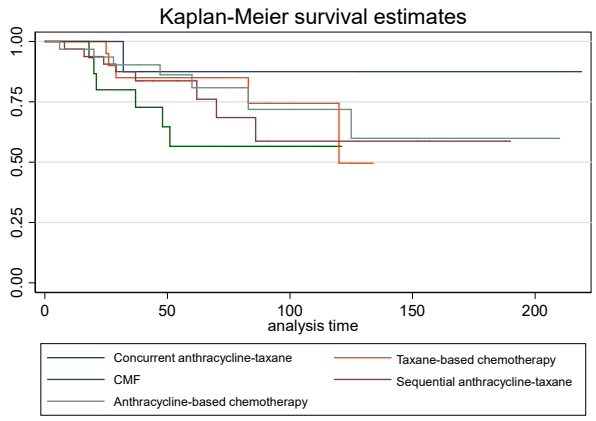

Figure 4. Overall survival curve disaggregated by regimen

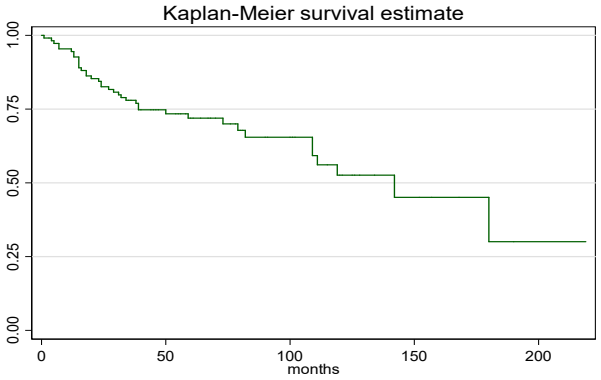

Figure 5. Disease-free survival curve for all patients

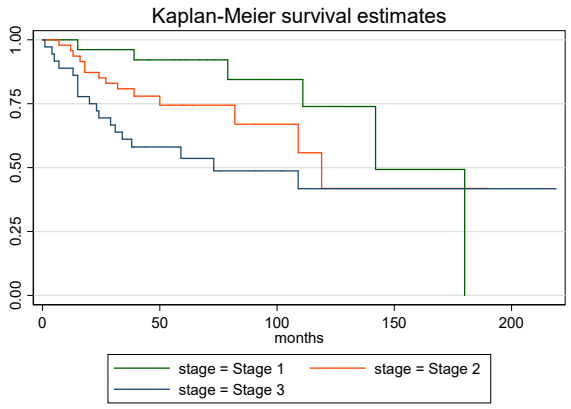

Figure 6. Disease-free survival curves disaggregated by stage

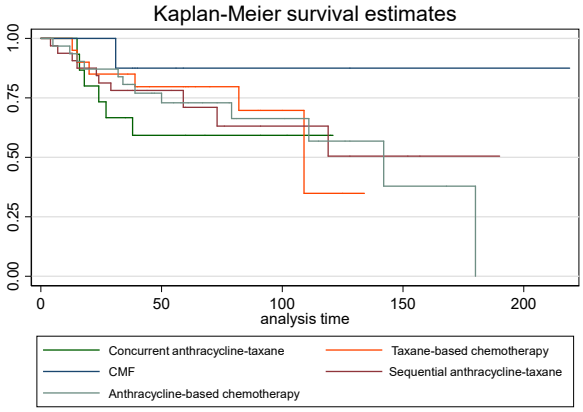

Figure 7. Disease-free survival curves disaggregated by regimen

compare survival outcomes of TNBC patients who do not receive adjuvant chemotherapy from those who receive chemotherapy.

The survival outcomes of patients with TNBC were worse with a higher stage of disease, with an increased risk of death in the first 5 years after diagnosis which is consistent with the findings of other studies[17-19]. Once disease recurrence developed, mortality quickly followed as evidenced by the 8 months median interval from disease recurrence, consistent with the previous literature[4].

The type of chemotherapy regimen did not predict overall survival and disease-free survival. Previous literature determined that anthracycline-based regimen had better overall survival compared to CMF regimen, but the difference was not statistically significant[16]. On the contrary, the present study revealed that the CMF regimen had the best survival outcomes, but the difference was likewise not statistically significant. The improved survival outcomes seen in CMF patients may be due to the small sample of patients given this regimen (N=8). Meanwhile, the poor survival outcomes seen in patients given concurrent anthracycline-taxane chemotherapy may be associated with the higher stage of disease of patients given this chemotherapy regimen.

Another important factor that was not considered in the present study was the impact of varying chemotherapy dosage on survival outcomes. According to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2012), an anthracycline-based regimen with higher cumulative doses had better survival outcomes when compared to standard dose regimen[11]. The dosage of chemotherapy regimen should be considered in further studies to define its' influence on survival outcomes.

The only variable that was able to predict mortality was histopathologic grade of the tumor, as patients with histopathologic grade 3 breast cancer had 3.5 times greater risk for mortality compared to patients with grade 1 cancer, indicating the importance of exploring the microscopic and molecular features of breast cancer subtypes as prognostic factors for survival. Nonetheless, a possible explanation for this finding is that the cohort was comprised mostly of patients with histologic grade 3 disease, which could have affected its' ability to predict mortality.

The difference in survival outcomes might have been influenced by the low sample size in the present cohort, which could have affected the reliability of conclusions made. There is a need for oncologists in the Philippines to work together on a multicenter study so that the association between various clinical factors and survival outcomes could be further elucidated.

Another important limitation of this study was the use of retrospective data. The patients who were included in the study may have certain characteristics that were

not reflective of the greater population. As such, the reliability of the study findings might have been affected by selection bias, as the researchers were dependent on the available medical data presented by the medical oncologists. This form of bias was minimized by following a strict inclusion and exclusion criteria in this study. Nonetheless, there is a need to conduct a large-scale prospective study that could expound on the survival outcomes of TNBC patients in the Philippines. A national cancer registry that can better reflect data from the population is needed to determine the major prognostic factors associated with specific cancer types and the efficacy of current treatment options.

Another possible bias that could have affected outcomes include information bias, where key patient and treatment-related data may not have been recorded by the attending medical oncologists. As such, there is a need for prospective studies that could capture the key patient and treatment-related information needed to elucidate the efficacy and safety of various treatment regimens in triple negative breast cancer.

The relatively large number of patients (N= 50) who were lost to follow up and who were not included in the analysis was another limitation of this study. Attrition bias might have affected the validity and reliability of study results. Further investigation is needed to find the reasons why patients do not follow up and devise ways on how to reduce dropout rates.

Moreover, a longer follow-up of 5 years might be conducted to accurately determine survival of TNBC patients. TNBC is a heterogeneous disease, with differing molecular and microscopic phenotypes[20-23]. Previous studies have indicated that TNBC patients who have a basal phenotype have decreased disease-free survival compared to patients who do not have the basal phenotype [21, 24-25]. Researchers should investigate further the molecular and microscopic features of breast cancer subtypes to clarify which features portend a poor prognosis. In conclusion, use of adjuvant chemotherapy with sequential anthracycline-taxane, concurrent anthracycline-taxane, CMF, anthracycline-based, and taxane-based regimens among stage I-III TNBC patients in Makati Medical Center resulted in comparable overall survival and disease-free survival. The use of immune checkpoint inhibitors presents a viable option in TNBC as demonstrated in the Impassion 130 and KEYNOTE 119 trials, and their efficacy should be further evaluated in the Philippine setting.[26-27]

Conflict of interest statement: The authors certify that they have no affilitations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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