The Prognostic Factors Influencing the Outcomes in Patients with Triple Negative Breast Cancer

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Abstract:

Introduction: Triple-negative breast cancer (TNBC) accounts for approximately 10% -- 17% of all breast cancer and characterized by a high proliferation rate and increased aggressiveness compared with other subtypes. Surgical intervention is a key component in the treatment of breast cancer. Cytotoxic chemotherapy represents the mainstay treatment and radiotherapy is a well established modality to improve loco regional control after surgery with positive impact on long-term survival in high-risk patients. In the literature, some prognostic factors reported to be associated with poor outcome in TNBC while others are not.

Aim of the study: Is to analyze the various clinico pathological prognostic factors associated with reduction in overall survival and disease recurrence free survival in these patients.

Patients and methods: This is a retrospective study enrolled patients received treatment and / or follow up in Sohag University Hospital, Egypt between 2019 and 2024 by surgery, chemotherapy and radiotherapy.

Results: The study enrolled 111 female patients both pre and post menopausal (55, and 56 respectively). The median age was at 48 yr. During follow up (mean at 30.8 m) disease recurrences and deaths were reported in 30 (28%) and 17 (15%) respectively with median times at 21.50 and 28 m respectively. A subgroup comprising only the patients treated with surgery, chemotherapy and radiotherapy (61 patients) was analyzed. In the whole cohort, disease recurrence free survival was significantly worse with neo adjuvant chemotherapy, advanced stage, multi focality of cancer lesions, presence of > 5 axillary lymph nodes pathologically infiltrated, extra capsular extension, peri neural infiltration, lympho vascular invasion, and level of Ki-67 labelling index ≤ 40% with p values at 0.012, 0.000, 0.003, 0.003, 0.016, 0.042 and 0.038 respectively while in the tri modality subgroup, a significantly worse outcome was associated with modified radical mastectomy, advanced stage, multi focality of lesions, and ki-67 labelling index ≤ 40% with p values at 0.013, 0.001, 0.000 and 0.011 respectively. On the level of overall survival, a significantly worse result in the whole cohort was associated with neo adjuvant chemotherapy, modified radical mastectomy, advanced stage, multi focality of cancer lesions, maximum tumor dimension > 4 cm, presence of > 5 axillary lymph nodes pathologically infiltrated, extra capsular extension and, peri neural infiltration with p values at 0.012, 0.016, 0.001, 0.024, 0.023, 0.001, 0.010 and 0.043 respectively. In the tri modality subgroup, a significantly worse results were associated with neo adjuvant chemotherapy, modified radical mastectomy, advanced stage and multi focality of lesions with p values at 0.040, 0.026, 0.025, 0.001 respectively.

Conclusions: This study provides further information on the relevance of chemotherapy timing, type of mastectomy, stage of the disease, multi focality of lesions, extra capsular extension, peri neural infiltration, peri vascular invasion, size of primary tumor and number of infiltrated lymph nodes as good predictors of survival and recurrence in triple negative breast cancer.

Key words: Prognostic factors, outcomes, triple Negative Breast Cancer.

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Introduction:

Breast cancer is the most common malignancy and the second cause of death by cancer in women worldwide. According to Cancer statistics 2020, it represents about 30% of female cancers [1]. In Egypt, breast cancer account for about 38% of all newly diagnosed cancer patients [2, 3].

This heterogeneous disease can be classified into four molecular subtypes (luminal A, luminal B, HER2 and triple-negative breast cancer (TNBC) according to the expression of the estrogen receptors (ER), progesterone receptors (PR), and the overexpression of the human epidermal growth factor receptor-2 (Her- 2) [4].

TNBC accounts for approximately 10% -- 17% of all breast cancer [5], often present as poorly differentiated tumors lacking expression of ER, PR, and HER2 on immune histochemical analysis; they are characterized by a high proliferation rate and increased aggressiveness compared with other subtypes [6].

Burstein et al. has suggested dividing TNBC into two major groups based on quantitative DNA expression , further categorized these tumors into four subgroups based on identified potential targets including the LAR group that expresses androgen receptors (AR) and cell surface mucin receptors (MUC1)—this subgroup alone constitutes group 1; the mesenchymal subgroup (MES) which expresses growth factor receptors such as platelet-derived growth factor receptor-α [PDGFRα] and c-Kit receptor; the basal-like immunosuppressed (BLIS)subgroup and, the basal-like immune-activated (BLIA) subgroup, which exhibits activation of the signal transducer and activator of transcription (STAT). The three subgroups; MES, BLIS, and BLIA formed group 2, as they had similar gene expression profiles [7].

Surgical intervention is a key component in the treatment of breast cancer and there are two primary types of breast surgery available: modified radical mastectomy (MRM) and conservative breast surgery (CBS). MRM was firstly proposed by Meyer and Halsted in 1894, and was commonly used in the past as a surgical treatment of breast cancer. More recently, CBS has developed as a well-recognized alternative to mastectomy for the treatment of early-stage breast cancer [8].

Despite the emergence of new biologic and targeted agents, cytotoxic chemotherapy (CT) represents the mainstay treatment for TNBC and its therapeutic benefits are well established in the neoadjuvant, adjuvant, and metastatic settings [9].

The third treatment modality in TNBC is radiotherapy (RT). It's well recognized that RT is able to improve loco regional control (LRC) in breast cancer patients both after CBS and MRM with positive impact on long-term survival in high-risk patients [10].

In the literature, some prognostic factors reported to be associated with poor outcome in TNBC like lympho vascular invasion (LVI), tumor size, lymph node involvement and, Ki-67 expression [11,12], while others like age and histological grade found not correlated with poor prognosis [13].

Our retrospective study aims to analyze the clinico pathological prognostic factors associated with reduction in overall survival (OS) and disease recurrence free survival (DRFS) in patients with TNBC received treatment and / or follow up in Sohag University Hospital, Egypt between 2019 and 2024 in order to define those factors associated with tumors with more aggressive behavior.

Patients and Methods:

Case Selection

This hospital-based retrospective study comprised subjects diagnosed with early/locally advanced breast adenocarcinoma of invasive duct subtype of any degree whose immunostaining showed lack of expression of ER, PR and Her-2.

Subjects from either sex aged between 18 and 80 years were included. The patients should have visited and or received treatment in Sohag University Hospital by surgery and or chemotherapy (CT) and or radiotherapy (RT) from January 2019 to December 2024, with adequate materials (slides, blocks and clinical records) and follow up period of at least 3 months.

Exclusion criteria included presence of metastatic disease at presentation, non invasive cancer, previous history of cancer, history of hormonal treatment and, organ failure. The subjects with TNBC were identified from the Hospital records, and the data regarding the clinical history, tumor characteristics, therapy and follow up visits were obtained from their clinical charts and by telephone communication with them.

Statistical analysis

The qualitative data were presented in frequencies and percentages and quantitative data were presented by mean (standard deviation [SD]) or median. The differences in clinico pathologic features, imaging characteristics and, treatment approaches between the various subgroups in the study were evaluated using an independent sample t-test / Mann-Whitney U test for quantitative variables and Chi-square / Fisher"s exact test for categorical variables. Disease recurrence free survival (DRFS) was measured from date of diagnosis to date of relapse/progression of disease or date of last follow up in months. Overall survival (OS) was measured from date of diagnosis until death or date of last follow up in months. Survival curves were produced by the Kaplan-Meier method and differences assessed by log-rank test. Cox proportional hazards test was used for multivariate analyses to identify variables significantly associated with DRFS and OS. All statistical analyses were performed using SPSS (version 22.0, SPSS Inc.). A two-tailed p value < 0.05 was considered statistically significant.

The study has received approval from The Medical Research Ethics Committee, Faculty of Medicine, Sohag University with IRB Registration number: Soh-

Med-24-08-01PD. Taking consent from the patients was exempted being a retrospective study.

Results:

A total of 111 patients with TNBC were identified. All patients were females. The ages at diagnosis have ranged from 26 to 80 yr with a median at 48 year and a mean at 50.48 year & SD: 12.30 year. The follow up periods ranged from 3 to 138 month (mean; 30.87 & SD: 20.44). During follow up, 30 (27%) recurrences encountered. Distant, local and nodal recurrences were reported in 26 (23%), 11 (10 %) and, 10 (9 %) cases respectively. The estimated median time to all recurrences was at 58 month (95% CI: 36.98 – 79.01). Death reported in 17 (15%) patients with an estimated median time at 89 month. (95% CI: 64.27 -- 113.72). The patients were divided into pre and post menopausal subgroups. Those who had no menstrual flow for 12 months were considered as postmenopausal while others were considered as premenopausal. A total of 55 patients (49.6%) were premenopausal and a total of 56 patients (50.4%) were postmenopausal. A significant difference was noted between the mean age in the premenopausal subgroup (40.07 year & SD: 6.00) and in the postmenopausal one (60.70 year & SD : 7.27 ; p = 0.000).

Table 1 compares between both subgroups in patients characteristics, disease characteristics, treatment modalities as well as in treatment outcomes (disease recurrence and survival)

It is evident from table 1 the significant association between arterial hypertension and the menopausal status of the patients. It was significantly more common in the older postmenopausal than in the younger premenopausal patients (p = 0.000). History of diabetes mellitus and body mass index (BMI) defined as the body weight divided by the square of the body height were not significantly different between both subgroups.

The imaging findings including the multi focality of the lesions and the Breast Imaging Reporting And Data System score (BIRADS) were not significantly different in both subgroups. Pathological features of the tumors including stage of the disease, grade, number of pathologically involved LN, maximum tumor dimension (MTD), and ki-67 labelling index were not significantly different between both subgroups.

Concerning the treatment modalities used, apart from the type of surgery, no other treatment modality has shown significant difference between both subgroups. As seen in table 1, significantly more MRM were done in the postmenopausal subgroup while more CBS were done in the premenopausal subgroup (p = 0.004). Post operative complications reported were not significantly different between both types of surgery. They included wound infection, seroma formation, hematoma and, flap necrosis in 3, 9, 4 and 2 patients respectively in MRM patients versus 2, 5, 3 and, 1 patients respectively in CBS patients (p = 0.655).

Regarding CT, in the whole cohort (111 patients), neoadjuvant chemotherapy (NAC) alone and, adjuvant chemotherapy (AC) alone were reported in 24 (21%) and 52 (47%) patients respectively while 27 (24%) patients have received both AC and NAC. Anthracyclin / Cyclophosphamide regimen was reported in 68.4% of cases while Taxane and Carboplatin / cisplatin (TC) regimen was reported in 14% of patients. FEC regimen consisting of 5-Flurouracil / Epirubicin / Endoxan was reported in only 1.7% of cases. From 2 to 6 cycles of NAC were given. In the AC setting, the Anthracyclin / Cyclophosphamide regimen was reported in 64 % of cases ranging from 1 to 6 cycles. Taxane / carboplatin regimen reported in 46% of cases both weekly (40%) and every 3 weeks (6%) . Xeloda was reported in 11% and FEC in 7 % of cases.

Prior to CT routine labs including complete blood picture, renal function and liver function tests were performed beside echo cardiography (at start in cases received anthracyclins). Patients consent were taken before CT. Side effects of CT reported in the whole cohort included hair loss (40%), leucopenia (28%), anemia (19%), thrombocytopenia (15%), peripheral neuropathy (11%), fatigue (10%), gastritis, vomiting (8%) for each and, diarrhea (5%) with no significant difference between both subgroups (p = 0.505).

As regards RT, adjuvant RT was given to 61 patients both after CBS (28 patients) and after MRM (33 patients) due to T3 tumors (14 patients) and N2 axillary LN (14 patients) while in 5 patients no complete data existed. A Varian linear accelerator 6 MeV energy was used. Three dimensional conformal technique was followed in all cases. As a routine work in our department, the patient was positioned on breast board with arms above the head. Simulation CT cuts were taken. Target volumes included all visible glandular breast tissue and lumpectomy cavity (in cases of boost irradiation) or chest wall in cases of adjuvant irradiation after MRM.

The volume routinely extended from the sternal head of the clavicle cranially to the loss of breast tissue caudally, from the ipsilateral edge of the sternum medially to the mid axillary line laterally and, from skin surface anteriorly to the pectoralis muscles and muscles of the chest wall posteriorly. Parallel-opposed tangential fields are used. A bolus of 3–5 mm is used daily over the chest wall or breast was used in cases of advanced T stage.

When irradiating the lymph nodes, the ipsilateral supraclavicular and axillary nodes from level I to III were irradiated through one anterior oblique photon field matched to the tangential fields. When the internal mammary nodes were irradiated, the tangential fields were usually crossing the midline. Organs at risk (OAR) include the heart, lung, other breast and liver were defined. Treatment plans were then generated, approved, and checked. Patients consent were taken.

Doses at 42.72 Gray / 16 sessions / 3, 1/5 weeks, 40 Gray / 15 sessions / 3 weeks and, 50 Gray / 25 sessions / 5 weeks were reported in 23 (38%), 22 (36%) and, 11 (18%) patients respectively. No definite data on doses were reported in 5 cases. When boost to the tumor bed was indicated, a dose at 10 Gray / 5 sessions / 1 week was usually given. Side effects due to irradiation

included mild to moderate fatigue, chest pain, skin erythema and itching in 60%, 40%, 40% and 25% of patients. Long term hyper pigmentation reported in 25% of cases.

On the level of treatment outcomes, both subgroups have shown similar proportions in disease recurrence and death with no significant differences as seen in table 1 and 2 respectively.

In order to minimize heterogeneity in the study population, a subgroup of patients comprises only those who underwent treatment by tri modality approach; surgery, CT and RT has been identified. This subgroup included 61 patients.

The clinico pathologic and the treatment related variables that could affect the treatment outcomes (both DRFS and OS) in the whole cohort and this subgroup have been analyzed and summarized in table 2 and 3 respectively.

It is evident from table 2 and 3 that the timing of chemotherapy has significantly affected both treatment outcomes in this study. On the level of the whole cohort, patients received AC and those received both AC and NAC have shown significantly better DRFS than those received NAC alone as seen in table 2 and figure 1.1 ($p = 0.012$) and also in OS in the whole cohort as seen in figure 2.1 ($p = 0.012$) and in the tri modality treatment subgroup as seen in figure 2.2 ($p = 0.040$).

Type of surgery also has also shown significant association with treatment outcome. Patients treated with CBS have shown significantly superior OS compared with patients underwent MRM in the whole cohort ($p = 0.016$) as seen in table 2 and figure 2.3 and also in the tri modality subgroup ($p = 0.026$) as seen in figure 2.4. On the level of DRFS, a significantly higher rate was observed in the tri modality subgroup in favor of CBS ($p = 0.013$) as seen in table 3 and figure 1.2

Among the clinico pathologic features that significantly affected the treatment outcomes is the stage of the disease. Advanced stage III was significantly associated with worse outcome compared with the earlier stage II not only in the whole cohort but also in the tri modality subgroup. As seen in figure 1.3 and 1.4, the DRFS is significantly lower in advanced stage in the whole cohort ($p = 0.000$) and in the tri modality subgroups ($p = 0.001$). Consistent with that was the OS that has shown significantly lower rates in advanced versus earlier stage of the disease across the whole cohort ($p = 0.001$) and the tri modality subgroup ($p = 0.025$) as seen in figure 2.5 and 2.6 respectively.

The multi focality of cancerous lesions has also demonstrated similar effects to that of the tumor stage on both treatment outcomes. A significantly lower DRFS rates was associated with multi versus uni focal cancers in the whole cohort ($p = 0.003$) and in the tri modality subgroup ($p = 0.000$) as seen in figure 1.5 and 1.6 respectively. On the level of OS, the same finding has been also observed with significantly lower rates in multi versus uni focal lesions both in the whole cohort as seen in figure 2.7 ($p = 0.024$) and in the tri modality subgroup as seen in figure 2.8 ($p = 0.001$).

Maximum tumor dimension (MTD) ranged from 1 to 10 cm with a median at 3.5 cm. Tumors whose maximum dimension was > 4 cm were associated with significantly lower OS rate than smaller tumors in the whole cohort ($p = 0.023$) as seen in figure 2.9.

The number of pathologically infiltrated axillary LN has ranged from 1 to 23 with a median at 5. A significantly worse DRFS and OS were observed with > 5 +ve LN versus =< 5 in the whole cohort as seen in table 2 and figures 1.7 ($p = 0.003$) and 2.10 ($p = 0.001$) respectively.

Presence of nodal extra capsular extension (ECE) has also negatively affected the DRFS and OS in the whole cohort as seen in table 2 and figures 1.8 ($p = 0.002$) and figure 2.11 ($p = 0.010$) respectively.

Presence of peri neural tumor infiltration (PNI) has also been observed to be associated with significantly lower DRFS ($p = 0.016$) and lower OS rates ($p = 0.043$) in the whole cohort as seen in table 2, figure 1.9 and 2.12 respectively.

Presence of LVI was also associated with worse DRFS in the whole cohort ($p = 0.042$) as seen in table 2 and figure 1.10.

The last predictive factor that significantly impacted the DRFS was the ki-67 labelling index. Indexes > 40% was significantly associated with better DRFS rates compared with those =< 40 in both in the whole cohort ($p = 0.038$) and in the tri modality subgroup ($p = 0.011$) as seen in figure 1.11 and 1.12 respectively.

Discussion:

TNBC is a BC subtype renowned for its capacity to affect younger women, metastasise early despite optimal adjuvant treatment and carry a poor prognosis. Patients with early-stage disease TNBC who do not achieve pCR after NAC should be offered from 6 to 8 cycles of adjuvant capecitabine monotherapy, in accordance with the CREATE-X trial. For patients with advanced disease who are PD-L1+, CD8+, or TIL+, optimal treatment would include up-front atezolizumab and nab-paclitaxel [14].

In the past AC has been the standard treatment for TNBC, but recently more and more patients with TNBC have NAC [15] as it allows for tumor downsizing, in vivo assessment of response to therapy, provides prognostic information based on pathological response [16]. It also allows early use of systemic therapy to eradicate occult distant micro metastasis [17]. However, it does not kill tumors when used for the first time as surgery does [15].

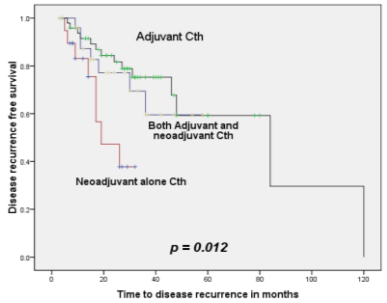

Figure 1.1. Impact of chemotherapy timing on DRFS in all patients

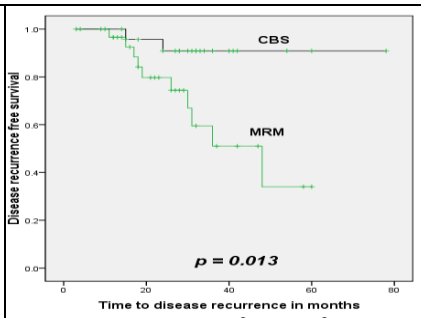

Figure 1.2. Impact of type of surgery on DRFS in 61 patients

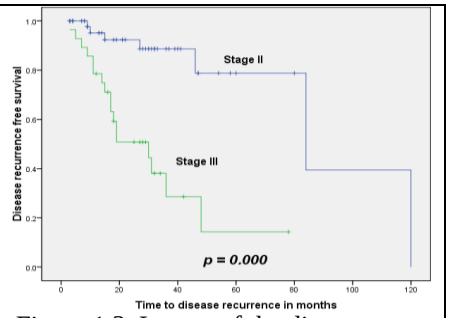

Figure 1.3. Impact of the disease stage on DRFS in all patients

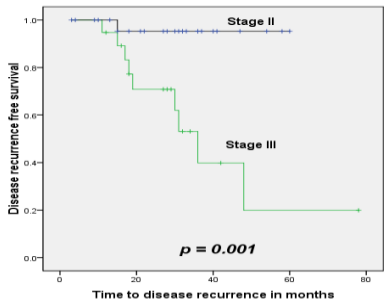

Figure 1.4. Impact of the disease stage on DRFS in 61 patients

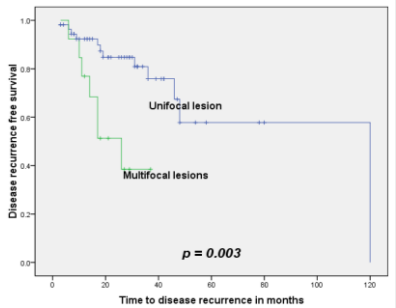

Figure 1.5. Impact of multifocality of lesions on DRFS in all patients

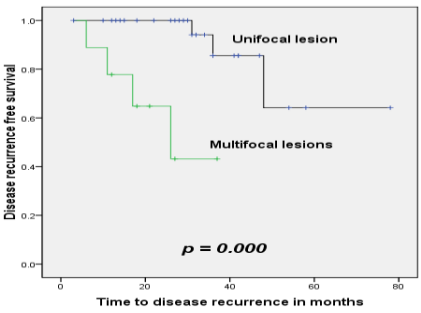

Figure 1.6. Impact of multifocality of lesions on DRFS in 61patients

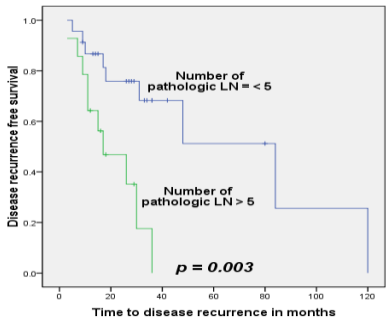

Figure 1.7. Impact of number of pathologic LN on DRFS in all patients

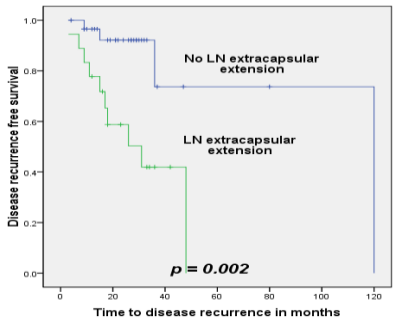

Figure 1.8. Impact of LN extracapsular extension on DRFS in all patients

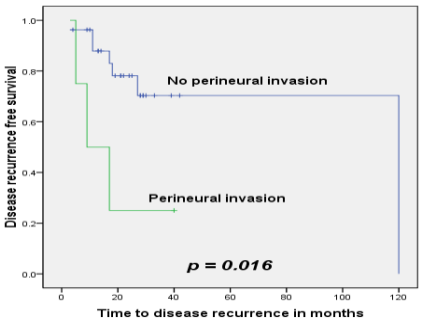

Figure 1.9. Impact of perineural infiltration on DRFS in all patients

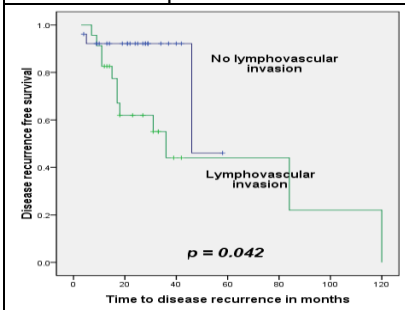

Figure 1.10. Impact of lymphovascular invasion on DRFS in all patients

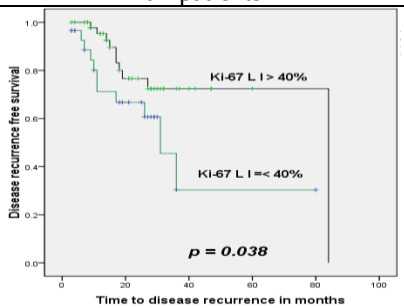

Figure 1.11. Impact of Ki-67 labelling index on DRFS in all patients

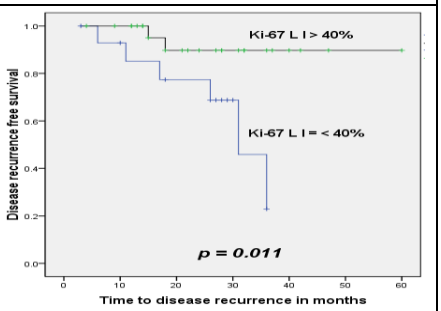

Figure 1.12. Impact of Ki-67 labelling index on DRFS in 61patients

Figure 1. Prognostic factors affecting Disease recurrence free survival (DRFS)

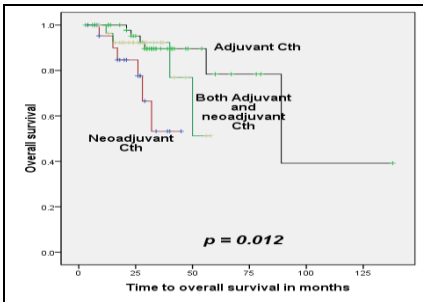

Figure 2.1. Impact of chemotherapy timing on OS in all patients

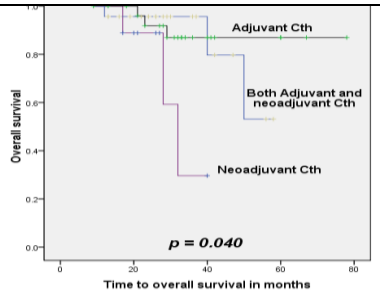

Figure 2.2. Impact of chemotherapy timing on OS in 61 patients

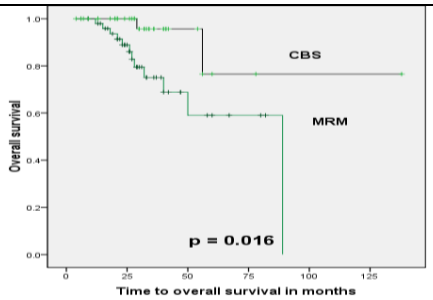

Figure 2.3. Impact of type of surgery on OS in all patients

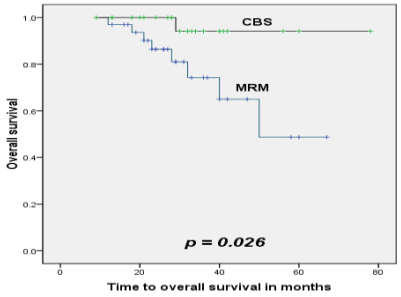

Figure 2.4. Impact of type of surgery on OS in 61 patients

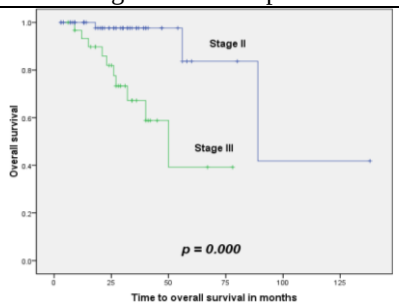

Figure 2.5. Impact of the disease stage on OS in all patients

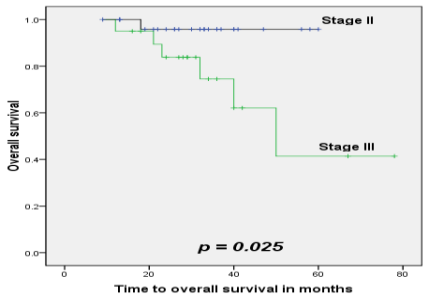

Figure 2.6. Impact of the disease stage on OS in 61 patients

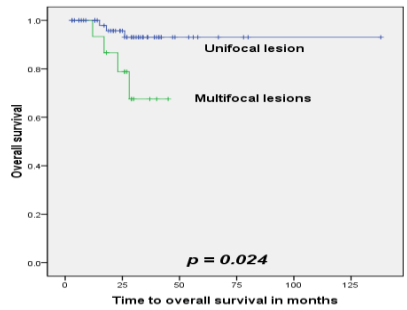

Figure 2.7. Impact of multifocality of lesions on OS in all patients

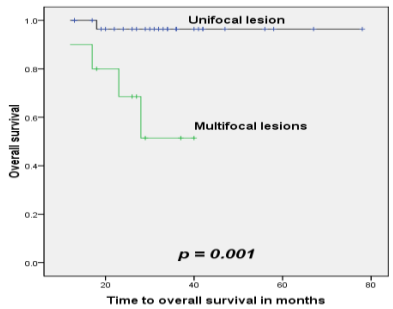

Figure 2.8. Impact of multifocality of lesions on OS in 61 patients

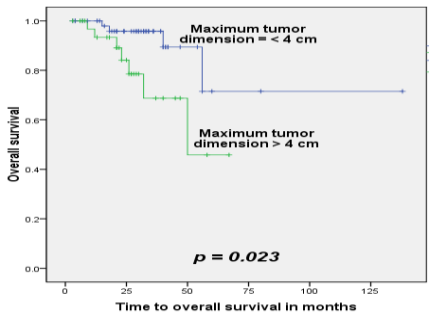

Figure 2.9. Impact of maximum tumor dimension on OS in all patients

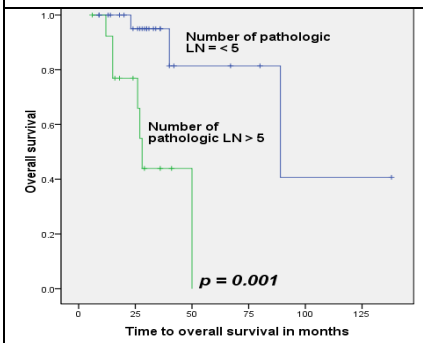

Figure 2.10. Impact of number of pathologic LN on OS in all patients

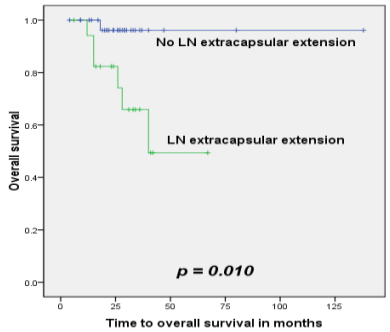

Figure 2.11. Impact of LN extracapsular extension on OS in all patients

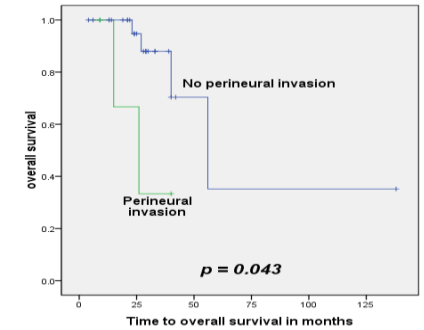

Figure 2.12. Impact of perineural infiltration on OS in all patients

Figure 2. Prognostic factors affecting Overall survival

Table 1: Clinico pathologic features of all patients based on menopausal status

Variable	Variable subgroups	Premenopausal (55 patients)	Postmenopausal (56 patients)	total	χ^2	*p* value
History of Diabetes mellitus	No	41 (53%)	25 (32%)	66	2.45	0.102
	Yes	4 (5%)	7 (9%)	11		
History of hypertension	No	42 (54%)	21 (27%)	63	12.37	0.000
	Yes	2 (2.6%)	12 (16%)	14		
BMI	=< 29.2	18 (30.5%)	11 (19%)	29	0.010	0.567
	> 29.2	19 (32%)	11 (19%)	30		
Multifocality of breast lesions	Unifocal	30 (40%)	30 (40%)	60	2.63	0.090
	Multifocal	11 (15%)	4 (5%)	15		
BIRADS	4	14 (23%)	14 (23%)	28	0.483	0.331
	5 - 6	20 (32%)	14 (23%)	34		
Stage of the disease	Stage II	29 (32%)	30 (33%)	59	0.130	0.446
	Stage III	14 (16%)	17 (19%)	31		
Grade of the disease	Grade II	26 (26%)	33 (33%)	59	0.497	0.308
	Grade III	21 (21%)	20 (20%)	41		
Maximum tumor dimension	= < 4 cm	28 (31%)	27 (30%)	55	1.023	0.214
	> 4 cm	14 (16%)	21 (23%)	35		
Number of pathologically affected LN	= < 5 LN	16 (43%)	8 (22%)	24	2.733	0.096
	> 5 LN	5 (13%)	8 (22%)	13		
Ki-67 Labelling index	=< 40%	15 (18%)	15 (18%)	30	0.161	0.431
	> 40%	25 (29%)	30 (35%)	55		
Type of Surgery	MRM	19 (20%)	34 (36%)	53	8.32	0.004
	CBS	27 (29%)	14 (15%)	41		
Type of chemotherapy	NAC	14 (14%)	10 (10%)	24	2.199	0.333
	AC	23 (22%)	29 (28%)	52		
	Both NAC&AC	16 (15%)	11 (11%)	27		
Radiotherapy	No radiotherapy given	2 (3%)	5 (7%)	7	1.739	0.180
	Radiotherapy given	33 (49%)	28 (41%)	61		
Disease recurrence	No	37 (34%)	41 (38%)	78	0.302	0.369
	Yes	16 (15%)	14 (13%)	30		
Overall survival	Censored	46 (42%)	46 (42%)	92	0.050	0.517
	Died	8 (7%)	9 (8%)	17		

BMI; body mass index. AC: adjuvant chemotherapy, NAC: neo adjuvant chemotherapy. MRM: modified radical mastectomy, CBS: conservative breast surgery.

Table 2. Variables affecting disease recurrence free survival (DRFS) and overall survival (OS) in all patients (Univariate analysis).

Variable	Variable sub groups & Patients included	Estimated mean DRFS in ms & SD (95% CI)	*P* value	Estimated mean OS in ms & SD (95% CI)	Patients included	*P value*
Type of chemotherapy	NAC (20) AC (49) Both NAC & AC (27)	21.75 & 2.54 (16.76 – 26.74) 72.43 & 11.00 (50.87 – 93.99) 43.41 & 4.47 (34.65 – 52.17)	0.012	35.26&3.13 (29.11 -- 41.40) 97.85&15.38 (67.69 – 128.00) 49.75&3.41 (43.05 – 56.44)	25 51 28	0.012
Type of Surgery	MRM (50) CBS (38)	54.94 & 6.21 (42.77 – 67.11) 82.56 & 12.78 (57.51–107.61)	0.426	65.87&6.31 (53.48 – 78.25) 117.57&17.57 (89.01 –146.13)	52 40	0.016
Radiotherapy	No radiotherapy given (7) Radiotherapy given (58)	72.14 & 24.14 (24.81–119.46) 57.65 & 4.96 (47.91 –67.39)	0.203	Not computed Not computed	7 61	---
Stage of the disease	Stage II (53) Stage III (28)	86.80 & 13.04(61.23–112.37) 31.68 & 5.61 (20.67 – 42.69)	0.000	103.20 & 16.41 (71.03 – 135.38) 50.93 & 6.54 (38.11 – 63.76)	57 31	0.000
BIRADS	= < 4 (26) 5 – 6 (33)	48.82 & 4.15 (40.68 – 56.96) 35.46 & 3.373 (28.85 – 42.70)	0.560	56.13 & 1.82 (52.56 – 59.70) 38.44 & 2.90 (32.74 – 44.13)	27 34	0.067
Multi focality of breast lesions	Unifocal (56) Multifocal (13)	82.70 &10.640 (61.85–103.56) 23.74 & 3.391 (17.09 –30.39)	0.003	129.79&4.58 (120.80 – 138.78) 37.22 & 3.26 (30.88 – 43.69)	60 15	0.024
Maximum tumor dimension	= < 4 cm (51) > 4 cm (30)	78.40 &10.84 (57.14 – 99.66) 41.65 & 4.591(32.66 – 50.65)	0.895	111.96 & 14.34(83.84 – 140.07) 49.47 & 5.31 (39.06 – 59.88)	55 34	0.023
Number of pathologic - ally affected LN	= < 5 LN (23) > 5 LN (14)	64.89 &13.744 (37.95 –91.82) 20.37 & 3.291 (13.92 –26.82)	0.003	98.55 & 17.30 (64.62 – 132.48) 34.11 & 4.87(24.56 – 43.65)	26 14	0.001
Extracapsular extension	No (30) Yes (18)	96.08 &16.948(62.86--129.29) 29.77 & 4.467 (21.01–38.52)	0.002	133.38 &4.52 (124.51– 142.25) 46.61 & 6.34 (34.17 – 59.05)	32 18	0.010
Peri neural invasion	No (27) Yes (4)	89.25 &11.859 (66.01-112.50) 17.75 & 6.777 (4.46 – 31.03)	0.016	78.34 & 22.81(33.63 – 123.04) 27.00 & 5.90 (15.42 – 38.57)	29 4	0.043
Lympho vascular invasion	No (26) Yes (23)	48.23 & 4.67 (39.09 – 57.39) 56.15 & 12.45 (31.73 –80.56)	0.042	Not computed Not computed	28 23	---
Pathologic response after NAC	CR (11) PR (15)	52.14 & 5.42 (41.51—62.77) 37.00 & 5.44 (26.23—47.67)	0.549	53.55 & 4.19 (45.34 – 61.76) 44.29 & 4.66 (35.15 – 53.44)	12 15	0.229
Grade of the disease	Grade II (55) Grade III (36)	49.82 & 7.39 (35.33 – 64.31) 97.55 & 8.85 (80.20 –114.90)	0.060	72.62 & 6.54 (59.80 – 85.44) 110.29 & 11.84 (87.08 –133.49)	58 40	0.362
Ki-67 Labelling index	=< 40% (29) > 40% (49)	39.16 & 8.47(22.56 – 55.77) 65.55 & 5.62 (54.53 –76.57)	0.038	68.15 & 5.39 (57.58 – 78.72) 65.18 & 8.52 (48.47 – 81.90)	30 54	0.901
Ejection fraction	= < 65 % (26) > 65 % (26)	49.00 & 9.44 (30.47– 67.51) 66.15 & 5.39 (55.58 –76.73)	0.123	62.32 & 7.71 (47.26 – 77.50) 64.33 & 7.70 (49.23 – 79.43)	26 27	0.190
Menopausal status	Premenopausal (51) Postmenopausal (51)	51.12 & 5.49 (40.36 – 61.89) 68.90 & 10.70 (47.92 –89.88)	0.337	65.12 & 4.15 (56.98 –73.26) 84.13 & 12.92 (60.59 – 108.28)	54 55	0.677
History of Diabetes mellitus	No (63) Yes (12)	76.34 & 9.78 (57.75 – 96.11) 44.25 & 3.50 (37.37 –51.12)	0.130	116.45 & 8.70 (99.39 –133.51) 44.25 & 3.50 (37.37 – 51.12)	63 11	0.870
History of hypertension	No (59) Yes (13)	87.60 & 9.58 (68.81 –106.39) 32.53 & 4.00 (24.68 – 40.39)	0.301	122.87 & 6.47 (110.18 –135.56) 39.22 & 2.18 (34.94 – 43.49)	61 14	0.462

AC: adjuvant chemotherapy, NAC: neo adjuvant chemotherapy, MRM: modified radical mastectomy, CBS: conservative breast surgery.CR: complete pathologic response, PR: partial pathologic response.

Table 3. Variables affecting disease recurrence free survival (DRFS) and overall survival (OS) in the tri modality subgroup (Univariate analysis).

Variable	Variable sub groups & Patients *included*	Estimated mean DRFS in ms & SD (95% CI)	*p* value	Estimated mean OS in Ms & SD (95% CI)	Patients *included*	*p* value
Type of chemotherapy	NAC (8) AC (27) Both NAC&AC (22)	27.43 &3.08 (21.39 –33.47) 59.74 &6.62 (46.76 --72.73) 45.69 &4.54 (36.78 --54.59)	0.565	31.51 & 3.07 (25.48 –37.55) 71.05 & 3.75 (63.70 -- 8.40) 51.00 & 3.31 (44.50 –57.50)	9 28 23	0.040
Type of Surgery	MRM (31) CBS (26)	40.83 &4.18 (32.64 –49.02) 72.67 &3.59 (65.63 –79.72)	0.013	50.71 & 4.55 (41.7 8 –9.64) 75.11 & 2.79 (69.63 –80.59)	33 28	0.026
Stage of the disease	Stage II (26) Stage III (19)	57.85 &2.09 (53.75--61.95) 40.00 &7.01 (26.26--53.74)	0.001	58.25 & 1.71 (54.89 –61.60) 53.64 & 7.31 (39.31 –67.97)	28 20	0.025
BIRADS	= < 4 (15) 5 – 6 (19)	54.29 &3.57 (47.27 ---1.30) 40.51 &3.32 (34.00 –47.03)	0.479	55.26 & 2.64 (50.09 –60.44) 39.11 & 3.29 (32.65 –45.56)	16 20	0.175
Multi focality of breast lesions	Unifocal (30) Multifocal (9)	65.22 & 6.56 (52.35 –78.09) 25.69 & 4.12 (17.60 –33.78)	0.000	75.85 & 2.10 (71.73 –79.98) 30.90 & 3.49 (24.04 –37.75)	32 10	0.001
Maximum tumor dimension	= < 4 cm (28) > 4 cm (20)	48.96 & 3.91(41.30 --56.63) 45.48 & 4.64 (36.37 –54.59)	0.952	56.13 & 2.62 (50.99 –61.28) 50.40 & 5.78 (39.06 –61.73)	31 20	0.074
Number of patho logically affected LN	= < 5 LN (13) > 5 LN (8)	40.13 &4.44 (31.42 –48.85) 28.92 &3.30 (22.46 –35.39)	0.076	57.38 & 6.05 (45.51 – 9.25) 40.43 & 6.90 (26.89 –53.97)	15 8	0.188
Extracapsular extension	No (18) Yes (12)	35.06 & 1.42 (32.22 –37.85) 36.71 &4.83 (27.23 –46.19)	0.282	38.77 & 1.18 (36.45 –41.10) 50.23 & 7.59 (35.35 –65.11)	20 12	0.274
Peri neural invasion	No (13) Yes (1)	Not computed Not computed	----	Not computed Not computed	15 1	----
Lymphovascular invasion	No (13) Yes (15)	Not computed Not computed	----	Not computed Not computed	15 15	----
Pathologic response after NAC	CR (8) PR (10)	Not computed Not computed	----	52.28 & 5.29 (41.91–62.65) 44.40 & 5.49 (33.6255.17)	9 10	0.460
Grade of the disease	Grade II (30) Grade III (21)	41.29 & 2.90 (36.61 –46.98) 68.14 & 5.13 (58.80 –78.20)	0.214	54.66 & 5.06 (44.74 –64.59) 70.57 & 4.84 (61.08 –80.07)	32 22	0.164
Ki-67 Labelling index	=< 40% (15) > 40% (27)	28.44 & 3.09 (22.36 –34.50) 55.53 & 2.99 (49.66 –61.40)	0.011	36.00 & 2.05 (31.96 –49.03) 51.76 & 3.70 (44.49 –59.03)	16 29	0.508
Ejection fraction	= < 65 % (15) > 65 % (15)	Not computed Not computed	----	Not computed Not computed	15 16	----
Menopausal status	Premenopausal (31 Postmenopausal (27)	56.87& 6.49 (44.14 – 69.60) 47.04 & 4.90 (37.43 –56.65)	0.938	64.73 & 4.85 (55.22 –74.24) 51.17 & 3.70 (43.91 – 58.444)	33 28	0.947
History of Diabetes mellitus	No (36) Yes (8)	Not computed Not computed	----	65.32 & 4.72 (56.07 –74.57) 42.85 & 3.83 (35.33-- 50.37)	38 8	0.896
History of hypertension	No (34) Yes (9)	61.14 & 6.07 (49.24 –73.04) 34.21 & 3.78 (26.62 –41.80)	0.576	68.03 & 4.09 (60.01 – 6.06) 38.93 & 2.42 (34.18 –43.69)	36 10	0.819

AC: adjuvant chemotherapy, NAC: neo adjuvant chemotherapy, MRM: modified radical mastectomy, CBS: conservative breast surgery. CR: complete pathologic response, PR: partial pathologic response. MRM: modified radical mastectomy, CBS: conservative breast surgery.

Table 3.1 The association between chemotherapy timing and both maximum tumor dimension (MTD) and peri neural invasion

Factors	NAC	AC	Total	x2	p
Maximum tumor dimension (MTD) = < 4 cm	6 patients	32 patients	38 patients	8.53	0.008
Maximum tumor dimension (MTD) > 4 cm	11 patients	12 patients	23 patients		
Perineural invasion +ve	3 patients	2 patients	5 patients	9.00	0.016
Perineural invasion -ve	1 patient	19 patients	20 patients		

Table 3.2 The association between type of surgery and maximum tumor dimension (MTD) and tumor stage.

Factors	MRM	CBS	Total	x2	p
Maximum tumor dimension (MTD) = < 4 cm	23 patients	27 patients	50 patients	5.60	0.030
Maximum tumor dimension (MTD) > 4 cm	20 patients	7 patients	27 patients		
Stage II	22 patients	28 patients	50 patients	10.05	0.002
Stage III	22 patients	5 patients	27 patients		

Table 3.3. The association between tumor stage and various pathologic factors and with the type of surgery.

Factors	Stage II	Stage III	Total	x2	p
Unifocal lesion	38 patients	13 patients	51 patients	7.41	0.010
Multifocal lesions	4 patients	8 patients	12 patients		
Extra capsular extension present	1 patient	13 patients	14 patients	23.13	0.000
Extra capsular extension absent	23 patients	4 patients	27 patients		
Lympho vascular invasion present	7 patients	14 patients	21 patients	7.42	0.009
Lympho vascular invasion absent	19 patients	7 patients	26 patients		
Ki-67 LI =< 40%	14 patients	13 patients	28 patients	4.52	0.031
Ki-67 LI > 40%	35 patients	11 patients	46 patients		
MRM	22 patients	22 patients	44 patients	10.05	0.002
CBS	28 patients	5 patients	23 patients		

Comparison between NAC and AC on the level of treatment outcome has given contradictory results. Three large randomized trials comparing NAC with AC (NSABP B-18, EORTC 10902, and IBBGS), found that there was no significant difference in survival between both of them [18, 19, 20].

However, these trials have been criticized for including many BC molecular subtypes in their populations. On the other hand, a large meta analysis conducted by Xia and colleagues that included 9 studies and 36,480 cases found that on the level of OS, it was poor with NAC compared to AC (HR = 1.59; 95% CI = 1.25–2.02; p = 0.0001). As regard to disease-free survival (DFS), there was no significant difference between both treatments (HR = 0.85; 95% CI = 0.54–1.34; p = 0.49). However, in case of pCR, NAC has significantly improved the OS (HR = 0.53; 95% CI = 0.29–0.98; p = 0.04) and DFS (HR = 0.52; 95% CI = 0.29–0.94; p = 0.03). In contrast, in patients with residual disease after NAC both the OS and DFS were significantly lower compared with AC (HR at 1.18; 95% CI = 1.09–1.28; p < 0.0001) for OS and at 2.36; 95% CI = 1.42–3.89; p = 0.0008 for DFS [15].

Consisting with that was a large retrospective study conducted by Bagegni N and colleagues on 19,151 patients with stages II and III TNBC treated with NAC or AC. They found that OS was inferior in patients treated with NAC compared to AC (73.4% [95% CI, 71.6–75.1%] vs. 76.8% [95% CI, 75.7–77.8%] p < 0.0001) [17].

Our results are in agreement with these studies. A significantly lower DRFS and OS were observed in the whole cohort in patients received NAC alone versus those received AC alone and those received both NAC and AC together (figure 1.1 and 2.1 respectively) and on the level of OS alone in the tri modality subgroup (figure 2.2). This observation could be attributed to the significant association between NAC and both the tumor size and peri neural invasion where more patients with larger tumors and peri neural invasion had been observed in the NAC group compared to the AC group (table 3.1).

During follow up the type of surgery showed significant impact on treatment outcome. The OS in the whole cohort was significantly better with CBS compared with MRM in the whole cohort and also in the tri modality subgroup (p = 0.016 & 0.026 respectively) as seen in figure 2.3 and 2.4 respectively. The same effect was also evident in DRFS in the tri modality subgroup (p = 0.013) as seen in figure 1.2. The worse association between MRM and both DRFS and OS could be attributed to the significantly higher number of patients with the more advanced stage (stage III) and more larger tumor sizes in this group compared with the CBS group as seen in table 3.2

The advantage of CBS over MRM in treatment outcome noticed in our study is matching with other studies that addressed the same point. Fancellu A and colleagues in a meta analysis included 19,819 patients with TNBC found that the pooled hazard ratio (HR) for OS was significantly lower for all cause mortality with CBS compared with MRM (HR: 0.78, 0.69 – 0.89) also on the level of distant metastasis (Odds ratio: 0.70, 0.53 – 0.94) along with an observed reduction in the odds of loco regional recurrence in favor of CBS [21]. Other meta analysis conducted by Wang SE and colleagues reported that patients underwent CBS are less likely to develop loco regional recurrence compared with MRM patients [22].

Another significant observation noticed in our study was the strong impact of tumor stage on the treatments results across the whole cohort and the tri modality subgroup as well. As seen in table 2, patients with stage III have had significantly shorter DRFS (p = 0.000) and OS (p = 0.001) compared with Stage II as shown in figure 1.3 and 2.5 respectively. In the tri modality subgroup similar results were observed where significantly lower DRFS and OS were observed in stage III versus stage II (p = 0.001 and 0.025 respectively) as shown in figure 1.4 and 2.6. This result is consistent with that reported by Silvana A and colleagues whose study on 841 TNBC patients found that the advanced stage was independent prognostic factor for mortality with hazard ratio at 3.13, 9.65, and 29.0, for stage II, III and IV respectively [23].

Among the prognostic factors that have been reported in the literature to be adversely affecting the treatment outcome is the multifocality of cancerous lesions. A large meta analysis conducted by Francisco E. and colleagues that enroled 22 and 67.557 women found that multifocality was associated with worse OS, DFS, and LRR at 5 years (OR 1.39, p = 0.02; OR 1.52, p = 0.02; and OR 3.23, p = 0.02, respectively) [24]. The results in our study are consistent with such observation. Multi focality of cancerous lesions was associated with worse prognosis compared to uni focality on the level of DRFS (p = 0.003) and OS (p = 0.024) in the whole cohort as seen in figure 1.5 and 2.7 respectively and also in the tri modality subgroup as observed in figure 1.6 and 2.8 (p = 0.000 and p = 0.001) respectively. This finding could be attributed to the significant association between multi focality of lesions and the advanced stage of the disease as shown in table 3.3.

Another pathologic factors that are intimately associated with tumor stage and found to be significantly impacting treatment results as well were the tumor size, number of pathologically infiltrated axillary LN, extracapsular extension, and, lympho vascular invasion. Concerning the tumor size, tumors whose maximum dimension was > 4 cm showed significantly worse OS versus smaller lesions (p = 0.023) as seen in figure 2.9.

A significantly worse DRFS was noticed with increasing number of infiltrated LN > 5 versus =< 5 in the whole cohort (p = 0.003) as seen in figure 1.7 and also on the level of OS as seen in figure 2.10 (p = 0.001).

Extracapsular extension was also significantly associated with advanced stage of the disease (table 3.3) and its presence was negatively impacting the DRFS and OS in the whole cohort as seen in figure 1.8 (p = 0.002) and figure 2.11 (p = 0.010) respectively. The same was also observed with lympho vascular invasion

whose presence was significantly associated with advanced stage as shown in table 3.3 and was associated as well with a significantly lower DRFS in the whole cohort (p = 0.042) as seen in figure 1.10. The worse outcome found in our study concerning these later two factors was also reported by Arora D and colleagues whose study on 141 TNBC patients observed that both extra capsular extension and lympho vascular infiltration had (among other factors) associated with significant decrease in OS and increase in hazard of death up to 9.71 (95% CI 2.27-45.45) for extra capsular extension and up to 3.72 (95% CI 1.13-12.35) for lymph vascular infiltration (p = 0.0026 & 0.0298 respectively) [25].

Peri neural invasion (PNI) was reported as a poor prognostic factor in a variety of cancers [26]. The frequency of PNI in invasive BC varies from 1.14% to 34.2% [27, 28, 29]. In a large case series on invasive BC, Nararyan and colleagues found that PNI was independent risk factor for loco regional recurrence [27]. In our study, PNI was observed in 5 cases (4%) and its presence was associated with poor DRFS and OS in the whole cohort as seen in table 2 and figures 1.9 (p = 0.016) and figure 2.12 (p = 0.043) respectively.

The last factor significantly impacted the treatment results in our study was the level of Ki-67 LI. Ki-67 is a nuclear non histone protein present in all active phases of cell cycle, except the G0 phase [30]. While high level of Ki-67 LI is well-established marker of poor prognosis in BC [31, 32, 33]. Its prognostic value remains controversial in TNBC [34].

While some investigators found that a high Ki-67 LI was associated with reduced disease-free survival (DFS) and OS in TNBC [35,36], others found no association between a high Ki-67 LI and prognosis [37 - 39]. And others concluded that high Ki-67 LI was associated with favorable prognosis in TNBC patients aged 50 or below [40].

In our study, indexes > 40 % were associated with significantly better DRFS in the whole cohort (p = 0.038) and in the tri modality subgroup (p = 0.011) compared with indexes =< 40% as seen in table 2 and 3 respectively and figures 1.11 and 1.12 respectively. This could be attributed to the significant correlation between the level of Ki-67 LI and the tumor stage. As seen in table 3.3, the majority of patients with LI > 40% (35 patients) has been in stage II versus only 11 patients in stage III (48% vs 15%; p=0.026).

Conclusion:

Although this study has some limitations due to its small size and retrospective design, we provide further evidence to other retrospective studies on the adverse impact of advanced clinical stage, tumor size, number of pathologically infiltrated lymph nodes, radical surgery, neo adjuvant chemotherapy, multi focality of lesions, extra capsular extension, peri neural infiltration and, perivascular invasion on patients survival and disease recurrence and we recommend these factors be utilized as prognostic determinants, and incorporated in the treatment decision making for TNBC after investigating the impact of these factors on treatment outcomes in larger studies.

Conflict of interest

The authors declare that there is no conflict of interest.

Authors′ contributions

First Author: Study design, writing and revision of the study.

Second author: Data collection, writing and revision

Third author: Revision, tables and figures editing.

Fourth author: Writing and revision.

Fifth author: Study design, data collection and writing.

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