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Time to Progression of Early Versus Advanced Breast Cancer in Iraq

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Abstract

Background: Breast cancer is the most common cancer in Iraq, in the latest Iraqi Cancer Registry report. Time to progression is an indicator method for primary endpoint in early and advance breast cancer stages.

Objectives: Comparison between early and advance breast cancers, and their characterizers, with calculation of time to progression of early versus advance stages.

Methods: A comparison retrospective analysis study included 702 women with early and advance breast cancer, at Baghdad Medical City, at period from January 2019 to May 2019. Applied of inclusion criterias, and exclusion criterias for selection. Descriptive statistics were calculated by used mean, standard deviation, and Chi-square. The odds ratio (OR) and to time to progression (TTM) used.

Results: The most common age was above fifth decade. Body mass index, as moderate obesity was prominent measuring. The IDC represented the most histopathology. The T2 was dominant stage, and N1 stage was the common. Women have early breast cancer presented in 54.9%, while advance cancer was 45.1%. The hormonal positive recorded more frequent, and invers was seen in the HER 2neu. Those comparison data were significantly difference among age, HR positive, and HR+/HER- subtypes. All linked data between early and advance stages to progression time by a logistic regression model were highly significant association. The time to progression in early stage was 46.7 months, and for advance was 31.3 months (P=0.001).

Conclusions: Comparison points between early and advance cancers reflect a novelty for our study. The interaction between early and advance stage to TTP give additional novelty as it is first end points in Iraqi breast cancer women.

Keywords: Early breast cancer;Advance breast cancer; Time to progression;Odds ratio

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Introduction

Breast cancer is common cancer in women, it is the leading cancer among women in both Europe and US and becoming an emerging oncologic disease in developing countries [1,2]. Every year more than 500,000 women die from breast cancer, making it the second leading cause of cancer-related deaths [1]. Globally breast cancer is the most common cancer, and the second most common cause of cancer related death in females [1,3,4]. Although breast cancer is the most common neoplasm in women, accounting for 26% of all cancers diagnosed annually. It is an important cause of morbidity and mortality despite recent developments in early diagnosis and management [4]. Early diagnosis is common in developed countries due to regular screening programs [3,5].

Iraqi Cancer Registry of Ministry of Health/Environment at 2011 recorded 3845 cases, 3763 were females and 82 were males [6]. Again, in Iraq 2011, the incidence was 18.96% with morbidity rate reached to 11.53% [7], but these data changed to 25.65% and 21.9% in 2014; 33.5% and 22.3% in 2015 according to WHO and Iraqi Cancer Registry [7,8]. According to GLOBCAN 2018, the new cases of BC was 2,088,849 (11.6%), with 626, 679 (6.6%) died cases overall all cancer sites [5].

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition (2018) defined early breast cancer (EBC) as stage I-II, and the stage III as locally advance [9,10]. The staging is the most important component on the prognosis than the other considerations. The higher the stage at diagnosis, the poorer the prognosis [10]. Stage I (and DCIS, LCIS) have an excellent prognosis and are generally treated with lumpectomy and radiation. Stage II and III with a progressively poorer prognosis and greater risk of recurrence are generally treated with surgery (lumpectomy or mastectomy with or without lymph node removal), chemotherapy (plus trastuzumab for HER2+ cancers) and sometimes radiation (particularly following

large cancers, multiple positive nodes or lumpectomy) [1,2,10]. Most patients with T1 or T2 which are early breast cancers present with a painless or slightly tender breast mass or have an abnormal screening mammogram [1,10,11]. Others may have breast tenderness, skin changes, bloody nipple discharge, or occasionally change in the shape and size of the breast. Rarely, patients may present with axillary LAP or even distant metastasis as < 20% [2,10]. Locally advanced breast cancer, most commonly refer to stage III disease, meaning advanced primary or nodal disease without clinically distant metastases. The criterias for staging considerations as locally advance breast cancer [1,10,12] are:

- T3 disease (tumors >5 cm) with involved lymph nodes
- N2 or N3 disease
- T4 disease with invasion into the chest wall (T4a); T4 associated with breast edema or skin ulceration or satellite nodules (T4b); T4 with both invasion and T4b characteristics (T4c); Inflammatory breast cancer (T4d)

As breast cancer growing, it may infiltrate or invade the dermis or the chest wall. The clinical course depends on several factors, including the characteristics at presentation, the biologic features, and the treatment given. Without treatment, all locally advanced breast cancers eventually metastasize to visceral organs and become life-threatening [1-4,12]. Local disease progression can lead to ulceration of the skin, pain, bleeding, and infection [4]. Inflammatory breast cancer is an important subcategory of locally advanced breast cancer that has a unique epidemiology, presentation, and biology. Inflammatory breast cancers are rare, accounting for only 2% of all breast cancers in the US [12,13].

Patients and Methods

Study Design

A comparison retrospective analysis study employed on 702 breast cancer patients were proven diagnosis by surgical histopathology reports. We reviewed all to extract relevant clinical variables including patient demographic features (age, residence, family history, smoking, educational level, and BMI), tumor clinical course (histopathology, TNM stages, hormonal status, HER2 neu, and molecular phenotypes), and therapy (surgical types, chemotherapy, hormonal, anti-HER2, and radiotherapy).

Settings

The study conducted on breast cancer patients diagnosed between 2015 and 2019, were data identified from the patient files at Baghdad Radiotherapy and Nuclear Medicine Center, Oncology Teaching Hospital, and National Cancer Center at Baghdad Medical City, Baghdad, Iraq, at period from January 2019 to June 2019.

Data collection

Data were collected from patients' files, and from patients at recruitment date. Structured data were exported from files when available were reviewed for patient and tumors characteristics, treatment regimens for primary, metastatic and clinical outcomes.

Eligible patients

All patients attending cancer centers were identified for registry, an exhaustive data base of incident tumors for patients consulting at these centers. During the same period, additional newly patients diagnosed with breast cancer were recorded in this study or were referred from outside centers to our centers for a second opinion and further treatment.

Inclusion criteria's

- Newly diagnosed breast cancer.
- Patients whom already on the treatment (chemotherapy, radiotherapy, hormonal therapy, and anti-HER2).
- Frequently visiting patients.
- Patients on follow up.

Exclusion criteria's

- Metastatic breast cancer at presentation.
- Already metastatic patients.
- Male breast cancer.
- Patients with a history of other malignant tumours.
- Patients with missing data.
- Loss of follow-up.

Statistical analysis

Descriptive statistics were calculated by used mean, standard deviation, and chi-square for equality of means between early and advance stages were computed before and after matching. A two-sided *P*-value of 0.05 or less was considered statistically significant differences for Fisher's exact, Pearson chi-square, Z-test, and F-test were used to compare the characteristics of patients with early and advance stages. The odds ratio (OR) is a statistic that quantifies the strength of the association between two stages in correlation to time to progression (TTP). Log-rank test have been used for comparisons among stages. The Kaplan-Meier method was used to estimate survival over stages. All data analyses were computed by using SPSS version 20.3.

Results

Demographic features

The distribution of demographic features was in Table 1. The most common age was belonging to group 51-60 years 261 (37.1%), followed by group 41-50 years as 158 (22.5%), 61-70 years as 137 (19.5%), with mean±SD= 48.8±10.6 years. Body mass index (BMI) of women, its' recording the moderate obesity was prominent measure in

Table 1: Demographic features of women in this study (n=702).

Variables		n (%)
Age (years) Mean±SD=48.8±10.5	20-30	25 (3.5)
	31-40	104 (14.8)
	41-50	158 (22.5)
	51-60	261 (37.1)
	61-70	137 (19.5)
	>70	17 (2.4)
	Total	702
BMI (m^2/Kg) Mean±SD=27.1±8.42	Underweight (<18.5)	5 (0.7)
	Normal (18.6-24.9)	71 (10.1)
	Overweight (25-29.9)	173 (24.6)
	Moderate obesity (30-34.9)	213 (30.3)
	Sever obesity (35-39.9)	185 (26.6)
	Morbid obesity (>40)	55 (7.8)
	Total	702

213 (30.3%), followed by sever obesity, and overweight, 185 (26.6%), 173 (24.6%), respectively. The normal BMI found in 71 (10.1%), while the two ends of BMI ranged in underweight and morbid obesity as 5 (0.7%), 55 (7.8%), respectively.

Breast cancer features

The IDC represented the most predominant histopathology in this study as 570 (81.2%). Furthermore, the ILC, and mixed were recorded in small proportions as 10.1%, 8.6%, respectively, as showed in Table 2.

According to the TNM staging of this study, the T2 was predominant stage 345 (52.6%), followed by T1, and T3 as 125 (19%), 118 (17.9%), respectively. The T4 stage only seen in 63 (9.6%). The results showed a high percent of N1 stage in 224 (33.8%) and was follow by N0 in 177 (26.8%), N2 in 163 (24.7%), and N3 in 97 (14.7%). Women whom have early breast cancer presented in 363 (54.9%), while those with advance stages were 298 (45.1%) of population, this illustrated in Table 2.

As shown in the table, the molecular subtypes found in different proportions (Table 2). The hormonal positive recorded more frequent than negative as 401 (66.4%), which was more than 203 (33.6%). Vice versa was seen in the HER 2neu, the negative more than positive as 355 (59.3%), 244 (40.7%), respectively. Regarding the molecular status of breast cancer, the HR+/HER- was the prominent one in this study as 309 (50.2%), followed by weak HR+/HER- in 184 (29.9%), triple-negative/basal-like 59 (9.6%), and HER2-enriched 49 (7.9%).

Breast cancer stages comparison results

The early stage patients, whose age was <50 years, were more frequent as 141 (21.3%) compared to advance stage 115 (17.4%). While age group >50 years, seen in 222 (33.6%) early, and 183 (27.7%) advance. Those comparison data were significantly difference (x^2=9.47, P=0.004). The HR was positive more evident in early 308(50.9%) than other demonstrations, with a significant difference, (x^2=46.65, P=0.0001). Among molecular subtypes, we found HR+/HER- with early stage in 163(26.5%), and with advance in 146 (23.7%) patients, other phenotypes in early as 199(32.4%), whereas in advance were 107(17.4%), with significant difference (x^2=9.57, P=0.001). There were no significant differences between early, and advance breast cancers regarding histopathology, and HER2neu (x^2=2.027, P=0.15); (x^2=3.05, P=0.08), respectively, as showed in Table 3.

Table 2: Breast cancer features of this study (n=702).

Variables		n (%)
Histopathology	IDC	570 (81.2)
	ILC	71 (10.1)
	Mixed	61 (8.6)
	Total	702
T staging	T0	6 (0.9)
	T1	125 (19)
	T2	345 (52.6)
	T3	118 (17.9)
	T4	63 (9.6)
	Total	657 (45 missing)
N staging	N0	177 (26.8)
	N1	224 (33.8)
	N2	163 (24.7)
	N3	97 (14.7)
	Total	661 (41 missing)
Stages	Early	363 (54.9)
	Advance	298 (45.1)
	Total	661 (41 missing)
ER, PR	Positive	401 (66.4)
	Negative	203 (33.6)
	Total	604 (98 missing)
HER 2neu	Positive	244 (40.7)
	Negative	355 (59.3)
	Total	599 (103 missing)
Molecular status	HR+/HER-	309 (50.2)
	HR+/HER- weak	184 (29.9)
	HER2-enriched	49 (7.9)
	Triple-negative	59 (9.6)
	Total	601 (87 missing)

Early versus advance on time to progression (TTP)

When we linked between early and advance stages to progression time by a logistic regression model that showed in Table 4. Age (OR=1.25; 95%CI=0.87-1.79; P=0.02), ER (OR=3.41; 95%CI=2.38-4.88; P<0.0001), and molecular subtypes (OR=1.6; 95%CI=0.43-0.83; P=0.002) have highly significant association to TTP in this study. However, BMI, histopathology, and HER2 neu reflected negative interaction between early and advance stage to TTP, with no significant differences in their results, (OR=0.66; P=0.1), (OR=0.33; P=0.15), (OR=0.33; P =0.08), respectively. We identified 363 (54.9%) women in early stage with TTP equal to 46.7 months, however, 298(45.1%) women in advance stage have TTP equal to 31.3 months. Those data showed significant difference in correlation at (x^2=10.14, P=0.001), as showed in Table 5, and Figure 1.

Discussion

Regarding age, we demonstrated women belong to the age <50 years 287(40.8%), and >50 years 415(59.2%), with a mean±SD (48.8±10.5 years). This is the same as results of Iraqi previous studies as Al-Naqqash et al. [14], Al-Alwan et al. [15], Al-Rawaq et al. [16]. In most Arabian countries, breast cancer is more commonly diagnosed

Table 3: Breast cancer stages comparison (n=702).

Variables		Early	Advance	x^2	*P*-value
		n(%)			
Age (years) (n=661)	**<50**	141 (21.3)	115 (17.4)	9.47	0.004
	>50	222 (33.6)	183 (27.7)		
Histopathology	**IDC**	299 (45.2)	240 (36.3)	2.02	0.15
	Others	59 (8.9)	63 (9.5)		
HR (n=604)	**Positive**	308 (50.9)	93 (15.4)	46.65	0.0001
	Negative	100 (16.6)	103 (17.1)		
HER 2neu (n=599)	**Positive**	138 (23)	106 (17.7)	3.05	0.08
	Negative	175 (29.2)	180 (30.1)		
Luminal status (n=615)	**HR+/HER-**	163 (26.5)	146 (23.7)	9.57	0.001
	Others	199 (32.4)	107 (17.4)		

Table 4: Early versus advance breast cancer stages on TTP.

Variables	Early	Advance	OR	Z-test	95% Cl	*P*-value
Age (years)	54.9%	45.1%	1.25	1.22	(0.87-1.79)	0.02
BMI (m^2/Kg)	55%	45%	0.66	1.64	(0.41-1.08)	0.1
Histopathology	54.2%	45.8%	0.33	1.42	(0.89-1.97)	0.15
ER, PR (n=604)	67.5%	32.5%	3.41	6.68	(2.38-4.88)	<0.0001
HER 2neu (n=599)	52.2%	47.8%	0.33	1.74	(0.96-1.85)	0.08
Molecular status (n=615)	58.9%	41.1%	1.6	3.08	(0.43-0.83)	0.002

Table 5: Time to progression (TTP) for early and advance stages.

Stages	n (%)	TTP (months)	x^2	*P*-value
Early	363 (54.9)	46.7	10.14	0.001
Advance	298 (45.1)	31.3		

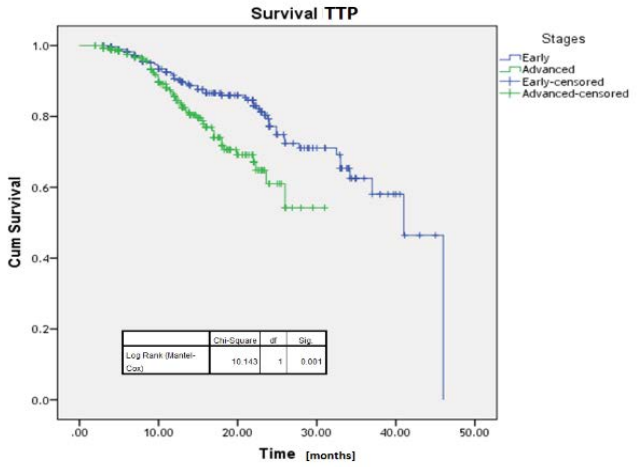

Figure 1: TTP curve for early and advance breast cancer.

in women with age of 50, which is consistence with our study, unlike the USA, where women aged 50 years and older are most commonly affected [17-19].

The BMI was normal 71 (10.1%), whereas the abnormal BMI represented in large percent included overweight 173 (24.6%), moderate obesity 213(30.3%), sever obesity 185 (26.6%), morbid obesity 55 (7.8%). Overall studies described BMI for breast cancer, our results were like Al-Naqqash et al. [14], and Al-Alwan et al. [15]. A pooled analysis studies demonstrated the risk of breast cancer to be 30% higher in women with a BMI over 31 m^2/Kg compared with women with a BMI of 20 m^2/Kg [1-4,11,17].

The IDC recorded in 570 (81.2%) of women as most common histopathology; the T2 345 (52.6%) presented as predominant T staging; the N1 stage 224 (33.8%), was the mostly N stages. All these are resembling the data of studies in our country, while differ from that recorded by Goldhirsch et al. [20]. The tumor size and lymph nodes staging are the most important prognostic factor and is directly related to surviva l [4,11,17].

A total of 363(54.9%) women were early breast cancer, while reminder 298 (45.1%) presented as advance stage. A combination of early detection, increased awareness, and improvements in management lead to these different percentages between early and advance stages.

The hormonal positive recorded more frequent than negative as 401 (66.4%), which was more than 203 (33.6%). Vice versa was seen in the HER 2neu, the negative more than positive as 355 (59.3%), 244 (40.7%), respectively. Regarding the molecular status of breast cancer, the HR+/HER- was the prominent one in this study as 309 (50.2%), followed by weak HR+/HER- 184 (29.9%), triple-negative/basal-like 59 (9.6%), and HER2-enriched 49 (7.9%). These results are most likely to Al-Naqqash study [14], and dislike with Al-Sarraf et al. [21]. Several studies have indicated that patients with hormonal receptors have a significantly higher survival rate, since positive status have benefits from hormonal treatment, where this not demonstrated in negative side [4,9].

The early stage ages were most frequent compared to advance stage, which was significantly difference (P=0.004). The ER, PR positive more evident in early than other demonstrations (P=0.0001). We found that molecular breast cancer subtypes in different frequencies and percentages with a significant difference (P=0.001) at HR+/HER-. While, there were no significant differences between early, and advance breast cancers among BMI, histopathology, and HER2 neu. Those results as whole not studied or recorded in our country, which represent a significant novelty for our study.

The second novelty was interaction between early and advance stage to TTP. The logistic regression model of our study linked between early and advance stages to progression time by odds ratio among age more than fifty years (OR=1.25; 95% CI=0.87-1.79; P=0.02), HR positive (OR=3.41; 95% CI=2.38-4.88; P<0.0001), and HR+/HER- subtype (OR=1.6; 95% CI=0.43-0.83; P=0.002), which have highly significant association between these variables to TTP in this study. The BMI (OR=0.66; P=0.1), histopathology (OR=0.33; P=0.15), and HER2 neu (OR=0.33; P=0.08), have no significant correlation between early and advance stage to TTP.

The length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body is describe as TTP. In a clinical trial, measuring the time to progression is one way to see how well a new treatment works [22]. Many recent studies have used TTP as the primary end points, and it have traditionally considered as surrogate end points for OS [23,24]. We identified that early stage TTP was 46.7 months, however, advance stage TTP was 31.3 months with significant difference (P=0.001). The Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials (STEEP) group pointed out that there is a lack of consistency in the definitions of many efficacy end points, and that definitions should be standardized to facilitate accurate communication among investigators, clinicians, regulatory agencies, funding agencies, clinicians, and patients, as well as exploratory cross-study comparisons[25,26]. The goal was to increase the quality of adjuvant breast cancer clinical trial conduct and reporting, while reducing the chances for miscommunication and misunderstanding on matters of interpretation of efficacy results from trials. That be achieved through the proposal of specific definitions on end points to be used in clinical trials on the adjuvant treatment of early and advance breast cancer. This additional novelty for our study, that we used TTP as first end points in Iraqi breast cancer women, which not previously mention in studies of the same design (To our knowledge, no similar proposals have been put forward to date regarding comparison between early and advanced breast cancer).

In our study, we were surprised to find that novelties, which lead to conclusion, that the TTP seem to be the primary end points most frequently used in contemporary in comparison between early and advanced breast cancer.

Conclusions

The IDC was most common histopathology; the T2 was predominant T staging; as early breast cancer. The hormonal positive recorded more frequent than negative, while invers in the HER 2neu. Comparison points between early and advance cancers showed significant differences. The early better than advance stage to TTP, with highly significant association between variables in this study. The novelty for our study, used TTP as first end points in Iraqi breast cancer women, which not previously mention in studies of the same design.

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