Treatment Options and Follow-Up among Iraqi Patients with Breast Carcinoma

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Abstract—Breast cancer ranks the first among the Iraqi population and the leading cause of cancer related female mortality. In addition to the barriers that impede early detection of that cancer other major challenges include the capacity for effective multimodality treatment.

Aim: To review and follow up a sample of Iraqi female patients diagnosed with breast cancer in a main referral center; recording their clinico-pathological characteristics, the offered treatment options and the rate of recurrence.

Material and Methods: This retrospective study analyzed the clinical and pathological characteristics of 230 Iraqi female patients histologically diagnosed with breast carcinoma who had reliable valid data related to their demographic, clinical and tumor pathological status. The studied parameters included the age of the patient, marital status, parity, age at first delivery, occupation, history of lactation and hormonal intake, family history of breast and any other cancer, histological type, tumor grade and clinical stage. Hormone receptors (Estrogen and Progesterone) and HER2 over expression contents of the primary tumors were evaluated immunohistochemically. The offered treatment options included surgery, chemotherapy, radiotherapy, hormonal and biological targeted therapy. The rate of recurrence was evaluated after a follow-up period of three years.

Results: Only 3.5% of the patients were under the age of 30 years while 39.1% were aged 50 years and over. About 84% were married, 11.3% were nulliparous, 24.9% had their first delivery before the age of 20 years and 56.9% were housewives. History of lactation was reported in 60.4%, whereas history of breast cancer was registered in 17.4%. The most common histological type of breast carcinoma was the infiltrative ductal (86.5%), well differentiated carcinomas were diagnosed in only 5.2%. The rates of positive ER, PR and HER2 tumor contents were 68.3%, 65.7% and 29.6% respectively. Overall 8.3%, 4.3%, 39.6% and 7.8% of the patients were diagnosed at stages I, II, III and IV respectively. Surgery was the primary treatment modality prescribed to the vast majority (96.1%) of the patients; 88.2% of those underwent modified radical mastectomy and only 3.6% had breast conservative surgery. Whereas 91.7% received chemotherapy, radiotherapy, hormonal and biological therapy were applied on 65.7%, 63.5% and 27.4% respectively. Recurrence of breast carcinoma three years following treatment was displayed among 9.7%; displaying significant direct association with the clinical stages of the disease (p<.05).

Conclusions: Breast cancer is still diagnosed at relatively advanced stages at the time of first presentation in Iraq; requesting radical mastectomy. Early detection represents the principal approach to control breast cancer in the near future. Regular long-term follow up through multidisciplinary tumor boards is mandatory to monitor response to therapy and recurrence.

Index Terms—Breast Carcinoma, Follow-up, Iraqi Patients, Options, Treatment.

I. INTRODUCTION

Whereas breast cancer is the most prevalent malignancy among women worldwide [1], in Iraq it ranks the first among the population and the leading cause of cancer related female mortality [1], Numerous studies from Iraq indicated that up to the present time a considerable rate of female patients still present with breast cancer at younger age groups with more advanced stages and aggressive tumor biological profiles compared to their western counterparts [3]- [9]; ultimately leading to unfavorable prognosis.

It has been reported that breast cancer is etiologically, genetically and histologically heterogeneous [10]. The World Health Organization has clearly documented that early detection of breast cancer when linked with adequate therapy could significantly reduce death from the disease in developing countries [11]. In Iraq, a national program for early detection of breast cancer has been initiated since 2001 [3]-[5], [8], [12]. Adding to the barriers that constantly impede early diagnosis of that cancer in the country, which have been comprehensively illustrated in earlier studies [13]- [19], other major challenges facing that project include the lack of evidence-based protocol guidelines associated with the limited capacity for effective multimodality treatment [4], [8], [12], [16], [20].

The dilemma of inadequate poorly accessible health services which leads to the crippling out-of-pocket healthcare expenditures contribute significantly to the low survival from the disease in low- and middle-income countries [21], [22]. Improving access to multimodality treatment of breast cancer should involve surgery, chemotherapy, adjuvant hormone and radiotherapy. In general, the choice of treatment is determined by many factors including the pathological features of breast cancer, the demographical and clinical characteristics of the patients and the risks of recurrence. The latter demands regular follow up to diagnosis any loco-regional relapse promptly. Limited research has been published in the literature of developing countries regarding the treatment options in the management of breast cancer and the follow-up of the affected patients [22]- [25].

This study was designed to follow up a sample of Iraqi patients diagnosed with breast cancer at a major tertiary health care center in Baghdad; recording their clinico-pathological characteristics, the offered treatment options and the rate of recurrence.

II. Materials and Methods

This retrospective study analyzed the clinical and pathological characteristics of 230 Iraqi female patients diagnosed with breast cancer. The studied variables were registered from the information system data base of the National Cancer Research Center, Baghdad University and the case sheet records of the Referral Center for Early Detection of Breast Tumors, Oncology Teaching Hospital in Baghdad throughout the year 2019.

Inclusion criteria comprised all female patients with histopathologically confirmed diagnosis of invasive breast carcinoma who have reliable valid follow up data related to their demographic, clinical and pathological status (for three years). Cases with non-invasive in situ carcinoma and those with missing information were excluded. Each patient in this study completed a written consent prepared and approved by the Ethical Committee of the National Cancer Research Center in accordance with the ethical standards of the declaration of Helsinki; allowing clearly the utilization of their relevant information for the purpose of research studies.

Demographic, clinical and pathological parameters included the age of the patient at the time of diagnosis, marital status, parity, age at first delivery, occupation, history of lactation and hormonal intake (for a minimum period of 6 months), family history of breast or any other cancer, WHO histological typing of breast carcinoma [26], tumor grade (following modified Nottingham Bloom Richardson) [27] and the clinical stage of the disease at presentation (defined according to the UICC TNM Classification System) [28]. Assessment of Estrogen and Progesterone receptors (ER, PR) and HER2 over expression contents of the primary tumors was carried out by Immunohistochemical (IHC) staining of the formalin fixed paraffin-embedded tissue blocks containing the breast cancer specimens utilizing (Dako) kits and specific monoclonal antibodies

The offered therapeutic options included the type of treatment (surgery, chemotherapy, radiotherapy, hormonal and biological). Assessment of the rate of recurrence after a follow-up period of three years was carried out through reviewing the patient's history, clinical examinations, imaging investigations and laboratory tests; recording the relationship with the clinical stages of breast cancer at the time of first presentation.

Statistical analysis of the studied variables was carried out using Statistical Package for Social Sciences (SPSS) version 25. Categorical data were presented by frequencies and percentages. Chi square test was used to assess the association between the recurrence of breast carcinoma and the stage of disease at diagnosis. A level of P value less than 0.05 was considered significant.

III. Results

TABLE I: The Demographic, Clinical and Tumor Parameters

Parameters	N	%
Age (years)		
< 30	8	3.5
30-49	132	57.4
=/>50	90	39.1
Marital status		
Currently married	194	84.3
Single	25	10.9
Divorced or widowed	11	4.8
Parity (n=204)		
No children	23	11.3
1 – 3	60	29.4
> 3	121	59.3
Age at 1st childbirth (n=181)		
< 20	45	24.9
20 – 29	97	53.6
≥ 30	39	21.5
Occupation		
Housewife	131	56.9
Employee	88	38.3
Retired	9	3.9
Student	2	0.9
History of Lactation		
Yes	139	60.4
No	91	39.6
Family History of Breast Cancer		
Yes	40	17.4
No	190	82.6
Family History of Other Cancers		
Yes	24	10.4
No	206	89.6
Histopathological Type		
Invasive ductal carcinoma	199	86.5
Invasive lobular carcinoma	16	6.9
Mixed	6	2.6
Others	9	3.9
Tumor Grade		
Well Differentiated	12	5.2
Moderately Differentiated	162	70.4
Poorly Differentiated	56	24.3
Estrogen Receptor		
Positive	157	68.3
Negative	73	31.7
Progesterone Receptor		
Positive	151	65.7
Negative	79	34.3
HER2 Over Expression		
Positive	68	29.6
Negative	162	70.4

Table I illustrates the demographic, clinical and tumor characteristics of the studied patients. The peak age frequency was noted among the age period (30-49 years); only 3.5% were under the age of 30 years while 39.1% were aged 50 years and over. Approximately 84% of the patients were married, 11.3% were nulliparous, about 25% had their first delivery before the age of 20 years and 57% were housewives. History of lactation was reported in 60.4%, whereas history of breast cancer and other cancers were registered in 17.4% and 10.4% respectively. The most common histological type of breast carcinoma was the infiltrative ductal (86.5%) followed by the lobular (6.9%). Well differentiated carcinomas were diagnosed in only 5.2% while the majority (70.4%) was graded as moderately differentiated. Positive ER, PR and HER2 overexpression contents of the primary carcinomas were confirmed by IHC assays in 68.3%, 65.7% and 29.6% respectively.

TABLE II: CLINICAL STAGES OF BREAST CANCER AT THE TIME OF DIAGNOSIS

Stage		N (n=230)	(%)	Total N (%)
I		19	8.3	19 (8.3)
II	IIA	66	28.7	102 (44.3)
	IIB	36	15.6	
III	IIIA	58	25.2	91 (39.6)
	IIIB	11	4.8	
	IIIC	22	9.6	
IV		18	7.8	18 (7.8)
Total		**230**	100	230 (100)

Clinical staging of the patients with breast carcinoma in this study revealed that overall 8.3% of the patients (19 cases) presented at stage I, whereas 44.3% (102 cases), 39.6% (91 cases) and 7.8% (18 cases) were diagnosed in stages II, III and IV respectively (Table II). Stage II was sub classified into IIA and IIB (28.7% and 15.6% of total respectively). On the other hand, stage III was further subcategorized into IIIA, IIIB and IIIC (25.2%, 4.8% and 9.6% of total respectively).

TABLE III: THE OFFERED TREATMENT OPTIONS IN BREAST CANCER MANAGEMENT

Treatment Modality	N	%
Surgery*	221	96.1
Chemotherapy	211	91.7
Radiotherapy	151	65.7
Hormonal	146	63.5
Biological	63	27.4

*Modified radical mastectomy was carried out in 195 patients (88.2%).

Treatment options were instructed by the examining surgeons and oncologists according to each individual condition (Table III). Surgery was carried out on 221 patients (96.1%); the majority (88.2%) underwent modified radical mastectomy and only 3.6% (8 patients) had breast conservative surgery. Two-hundred and eleven patients (91.7%) received Chemotherapy while Radiotherapy sessions were designed for 151 cases (65.7%). According to the results of IHC, hormonal therapy (Tamoxifen and Aromatase inhibitors) was offered as an adjuvant treatment option in 146 patients with ER and/or PR positive tumor contents (63.5%); whereas Herceptin was prescribed to 63 patients (27.4%) who had HER2 positive results.

TABLE IV: ASSOCIATION OF RECURRENCE WITH BREAST CANCER STAGES

CLINICAL BC STAGE (TN=230) N (%)		RECURRENCE (TN=217) * Yes No N (%) N (%)		TOTAL** N (%)
I 19 (8.3)		0	19 (100)	**19 (08.3)**
II 102 (44.3)	IIA 66 (28.7)	0	66 (100)	**102 (44.3)**
	IIB 36 (15.6)	2 (5.6)	34 (94.4)	
III 91 (39.6)	IIIA 58 (25.2)	5 (8.6)	53 (91.4)	**91 (39.6)**
	IIIB 11 (4.8)	2 (18.2)	9 (81.8)	
	IIIC 22 (9.6)	6 (27.3)	16 (72.7)	
IV 18 (7.8)		6 (33.3)	12 (66.7)	**18 (07.8)**
TOTAL		**21 (9.7)**	**196 (90.3)**	**230 (100)**

*Total number of studied cases; 13 out of 230 cases (5.7%) had missing information regarding the recurrence state
.**Chi Square statistic is 16.2252. The p value is .00102. The result is Significant at p < .05.

Overall, recurrence of breast carcinoma following treatment was displayed in 21 patients (9.7%) during the three-year follow up period of the study. The relationship between the clinical stage of breast cancer at the time of presentation and the recurrence state was significant at p <

.05. (Table IV). Whereas no patient diagnosed at stage I and IIA had any recurrence, 5.6%, 8.6%, 18.2% and 27.3% of patients presenting in stages IIB, IIIA, IIIB and IIIC respectively had positive relapse of the disease. On the other hand, recurrence was observed in one third of the patients diagnosed with stage IV (6 out of 18 cases).

IV. DISCUSSION

The demographic and clinical profiles of breast cancer in this study clearly illustrate the prevalence among premenopausal women; where the peak age frequency is noted in the middle aged groups. That finding was emphasized in numerous studies from Iraq [2]-[6], [8], [9], [12], [16]-[19]; and other developing countries [11], [21]-[25]; probably reflecting the younger age pyramid of the populations in these regions of the world compared to the developed countries where breast cancer is typically a disease of postmenopausal women. A comparative study on the characteristics of breast cancer in Iraq and the United Kingdom revealed that Iraqi patients were significantly younger [1]; justifying the initiation of screening programs for that type of cancer earlier [16], [18]- [22], [29].

Contrary to the clinical presentation of breast cancer reported in western studies [30]- [32] our data indicate that the majority of breast cancer in Iraq affect married multiparas women; interestingly, one quarter have delivered their first child in their teen ages and about two thirds had history of lactation. These results confirm the findings recorded in earlier Iraqi surveys [3], [4], [6], [16], [18], [19]; supporting the hypothesis that breast cancer is genetically heterogeneous and that racial disparities are reflected in the biological behavior of the disease in different societies [4], [33], [34]. The relatively high family history of breast cancer observed in this study and other published series from Iraq [3], [6], [16], [29], [35] recommend active promotion of public awareness and regular follow up among the target female population to identify promptly the high risk groups for breast cancer control.

The treatment options were modified in this study according to the tumor characteristics and the clinical stage at diagnosis. Pathologically, the histological and IHC profiles correspond to those reported in previous studies from Iraq; where moderately invasive ductal carcinomas predominate [3]- [5], [7]- [9] Compared to research on western patients, the lower rates of hormone receptor positive tumor contents coupled by the significantly higher HER2 over expressions among Iraqi patients reflect the predilection towards more aggressive behavioral forms of breast cancer [3], [4], [7], [9], [36], [37]. The dilemma of late stage at breast cancer presentation in Iraq and other developing countries has been the focus of many studies [3]-[9] which addressed several patient and health system-mediated barriers to early detection of the disease aiming to develop appropriate control strategies [11]- [24], [38], [39]. The lack of public education about breast health care in low- and middle- income countries reflected by the remarkable gaps in the knowledge regarding breast cancer urged the necessity to establish protocol guidelines for early detection and treatment of the disease stratified according to the level of available resources [16], [40].

In addition to the lack of access to affordable quality multimodality treatment options, the high mortality from breast cancer in developing countries is significantly linked to the stigma and associated societal implications of mastectomy which discourage women from seeking prompt medical care [22], [24]. Surgery as the primary treatment modality was prescribed to the majority of the patients in this study (96%). A critical review on mastectomy practice documented that although it is no longer considered a first-line choice for treating all breast cancers; nevertheless, it is still adopted as a principal procedure in the management [41]. It is regrettable to note that modified radical mastectomy is the standard surgery in Iraq [3], [7], [20] and other developing Arab countries [21]- [23]. where most of the patients are detected at late stages and the established radiotherapy centers have limited capacity for sophisticated conservative approaches [42]. Significantly higher rates of practicing breast conserving surgery are reported in studies from developed countries [42], [43]. It was found that in the presence of standard radiotherapy facilities there was no significant difference in survival among patients who underwent mastectomy versus those who had breast conservative surgery although many preferred mastectomies due to the fear of recurrence [43].

As invasive breast carcinomas require postoperative radiotherapy, 65.7% of the patients in this study were offered that treatment option in well-equipped units free of charge. Nevertheless, during the period of the study 8.8% did not continue treatment. Excluding financial causes, discontinuation of breast cancer therapy after initiation is often attributed to the associated side effects, long waiting lists or psychological factors [21]- [24], [44]. In a literature analysis on the trends in the management of breast cancer it was displayed that modern radiation therapy is available only in select centers in the Arab countries; recommending investment in technical equipment and human resources to overcome that shortage and its negative effects on the feasibility of novel treatment approaches [23].

The high rate of patients who received systemic chemotherapy in this study (91.7%) is obviously attributable to the advantages of free treatment services which are offered in all public hospitals across the country. As approximately half of the cases in the present study were diagnosed in advanced stages, the treatment was initiated with Anthracycline-based chemotherapy and the patients were monitored regularly by blood chemistry profiles and complete blood count tests. In those with hormone receptor positive tumors, 63.5% had Tamoxifen and/or Aromatase inhibitors as effective adjuvant endocrine therapy; while neoadjuvant hormone therapy was applied on nine patients who were not candidates for chemotherapy due to medical reasons. Due to the relatively high rate of HER2 positive breast cancer expressions among Iraqi patients observed in this study and others [3], [4], [7], [9], [36], [37], targeted biological therapy (Herceptin) was offered freely to 27% of the patients. These treatment protocols were almost in line with the recommendations of the breast health global guidelines for multidisciplinary integrated approaches to breast cancer management in limited resource settings [40], [45].

The relatively short period of follow-up in this study, compared to others [46]- [48], displayed a modest recurrence rate of breast carcinoma, in the form of local and regional relapses; that had significant direct association with the clinical stage of the disease at the time of diagnosis. It has been concluded that the most important factors associated with breast cancer recurrence are the size of the tumor and the axillary nodal involvement [47] whereas the clinical stage is considered predictive for estimating long-term survival [48].

In conclusion, breast carcinomas are still diagnosed at advanced stages at the time of initial presentation in Iraq; requesting radical mastectomies and palliative treatment. Early detection is the principal approach to control breast cancer in the near future. Multimodality treatment and long regular follow-up through multidisciplinary tumor boards are mandatory to monitor the response to therapy and avoid recurrence. Partnerships of cancer centers belonging to high income countries with those in limited resource nations could serve as a feasible approach to cancer control and research [49].

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript

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