World Journal of Breast Cancer Research

Editorial
Published: 12 oct, 2018

Tumor Characteristics of Female Breast Cancer: Pathological Review of Mastectomy Specimens Belonging to Iraqi Patients

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Editorial

Cancer is a major cause of mortality in the developing Eastern Mediterranean Region (EMR), where breast cancer constitutes the most registered female malignancy and the most common cause of cancer related deaths among women [1,2]. The World Health Organization reveals that the incidence rates of breast cancer are steadily increasing in countries of the EMR including Iraq, with annual rise ranging between 1% to 5% [3]. While cancer is the second killer among the general Iraqi population after cerebrovascular diseases, the breast continues to be the most prevalent site of malignancy nationwide over the past three decades [4]. In 2013 breast cancer accounted for 19.4% of all newly diagnosed cancers, 34.7% of female malignancies and 22.5% of cancer related deaths among Iraqi women [5]. Overall during that year 4,529 new female breast cancer patients were registered forming an incidence rate of 26 /100,000 female population, and 909 women died from that disease due to late diagnosis and inadequate management [3-5]. Iraqi studies indicate that the highest incidence rates of breast cancer are most frequently observed among middle aged women and that more than 40% of the cases are still detected at advanced stages [6-9].

It has been well documented that early detection of breast cancer when linked with adequate treatment could significantly reduce mortality irrespective of the biological nature of the tumor [2,3,10,11]. On the other hand, it is believed that the biology of breast cancer could reflect racial and ethnic disparities in survival from the disease [12]. The present manuscript highlights the pathological profile of breast cancer in Iraq through reviewing the characteristics of the tumors and their receptor defined subtypes in mastectomy specimens belonging to patients referred to the National Cancer Research Center in Baghdad.

The studied parameters comprise the histologic type, grade, tumor size, lymph node status, stage of breast cancer at presentation, Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal growth factor Receptor 2 (HER2) contents of the primary tumors and the receptor-defined surrogate subtypes. Breast carcinoma are typed histologically according to WHO, the tumor grade is defined following modified Nottingham Bloom-Richardson, while the stage of the disease is classified in accordance with the TNM system [13-15]. Assessment of ER, PR and HER2 contents of the primary tumors is carried out by Immunohistochemical (IHC) staining of the formalin fixed paraffin-embedded tissue blocks utilizing specific monoclonal antibodies; thus designating four main receptor-defined subtypes: Luminal A (ER/PR Positive/HER2 Negative); Luminal B/Triple Positive (ER/PR Positive/HER2 Positive); HER2 Enriched (ER/PR Negative/HER2 Positive) and Triple Negative (ER/PR Negative/HER2 Negative).

Focusing on Iraqi patients in a comparative study involving 1,940 Iraqi and British women diagnosed with invasive breast cancer, it was displayed that infiltrative invasive Ductal carcinoma was the most frequent histological type (86.5%) followed by Lobular carcinoma (8.8%) [16]. Well differentiated carcinomas were registered in only 6.7% of the examined mastectomy specimens, while 67.6% and 25.7% were graded as II and III. At the time of initial diagnosis only 20.5% of breast cancers measured 2 cm or less in diameter and lymph node involvement was noted in more than two-third of the patients (68.3%); thus classifying 12%, 47.5%, 31.9% and 8.6% patients into stages I, II, III and IV respectively (Table 1).

The frequencies of positive ER, PR and HER2 tumor contents were equivalent to 69.2%, 66.7% and 29.2% respectively; corresponding to the following rates of breast cancer subtypes: Luminal A (47.4%), Luminal B (13.7%), HER2 enriched (10.7%) and Triple Negative (14.7%). The trend of

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Received Date: *23 Sep 2018*
Accepted Date: *10 Oct 2018*
Published Date: *12 Oct 2018*

Citation:
Alwan NAS. Tumor Characteristics of Female Breast Cancer: Pathological Review of Mastectomy Specimens Belonging to Iraqi Patients. World J Breast Cancer Res. 2018; 1(1): 1006.

Table 1: Tumor Characteristics of Iraqi Female Breast Cancer.

Iraqi Breast Cancer Characteristics	% Distribution
Histologic Type	
IDC (NOS)	86.5
ILC	8.8
Mixed	2.2
Others	2.5
Tumor Size	
T1	20.3
T2	59.3
T3	15.9
T4	4.6
Lymph Node	
N0	31.7
N1	31.8
N2	21.7
N3	14.8
Histologic Grade	
I	6.7
II	67.6
III	25.7
Stage	
I	12
II	47.5
III	31.9
IV	8.6
Estrogen Receptor (ER)	
Positive	69.2
Negative	30.8
Progesterone Receptor (PR)	
Positive	66.7
Negative	33.3
HER2 Status	
Positive	29.2
Negative	70.8
IHC Subtypes	
Luminal A (E+/P+/HER2-)	47.4
Luminal B (E+/P+/HER2+)	13.7
HER2 Enriched (E-/P-/HER2+)	10.7
Triple Negative (E-/P-/HER2-)	14.7
Others	13.5

the Iraqi patients to present at advanced stages III and IV (40.5%), compared to their British counterparts (3%), was reflected by significantly larger tumors that were accompanied by frequent lymph node metastasis and by worse receptor defined phenotypes; illustrated statistically in higher rates of Triple Negative, Her2 Enriched and Triple Positive subtypes ($p < 0.001$). These significant differences in tumor characteristics between the two populations were maintained even after adjusting for age among premenopausal patients in both series. Although, higher frequencies of large breast cancers (T3,T4) were encountered in younger patients under the age of 50 years, yet no statistical association was noted between the age of the Iraqi patients and the pathological stage of breast cancer at presentation. On the other hand, nodal involvement was more prominent among younger age groups who yielded statistically higher HER2 positive tumor expressions.

Identical findings were documented in comparative studies targeting breast cancer patients from developing *vs.* well developed countries. Earlier reports have highlighted that African and Middle Eastern patients (including Iraqi women) are more likely to have ER/PR negative/HER2 positive tumor contents than their counterparts from developed western societies; suggesting variations in the biology of breast cancer among populations exhibiting younger age structures in low-middle income resource settings [17-21]. In a recent survey that was conducted to correlate the composite stage of breast cancer at the time of diagnosis in Iraq with other pathological parameters a highly significant correlation with the IHC subtypes was observed; where 64.4% of patients exhibiting Luminal A tumor patterns were diagnosed at early stages (I and II) while 68% and 62% of those with Triple Negative and Her2 Positive subtypes respectively presented at advanced stages (III and IV) [8].

Several other reports have triggered the public concern on the burden of breast cancer in Iraq; highlighting the dilemma of young age and late stage at presentation with the likely prevalence of aggressive tumor behavioral forms and illustrating the gaps in the knowledge and attitudes towards cancer in the community [4-9,16,22-26]. Nevertheless, it is worthwhile mentioning that Iraqi professionals are currently witnessing a regression in breast cancer stages among their patients following the initiation of the National Program for Early Detection of Breast Cancer in 2010 and after establishing the relevant protocol guidelines on early detection and public awareness [8,16,23,27]. That initiative was hindered earlier by the repercussions of the successive wars, conflicts and civil displacements in Iraq which led to disruption of the health care infrastructure, deficiency in the specialized manpower and financial constraints [9].

While the favourable tumor stages encountered at diagnosing breast cancer among western societies reflect the fruitful outputs of the nationwide mammography screening programs, the challenges to early diagnosis and treatment of the disease in developing countries signify problems of access to medical care; since 30% to 80% of their patients still present at stages III and IV [2,12,28,29]. On the other hand, the racial variations in the tumor characteristics point out to heterogeneity in the biological features of breast cancer; emphasizing the necessity of molecular genotype analysis for the study of ethnic disparities and the role of surrogate subtypes in breast cancer therapy.

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