ORIGINAL ARTICLE

Clinical and Histopathological Parameters of the Patients with Breast Cancer from North West Pakistani Population

Asif Ali[1], Mushtaq Ahmad[2], Nabila Javeed[3], Muhammad Ijaz[4], Mah Muneer Khan[5], Rauf Khattak[6], Mazhar Khan[7], Syeda Afsheen Hasnain Daud[8], Asma Fayyaz[9], Muhammad Naseem Khan[10], Abdul Salam[11], Zoufishan Rahat[12], Maham Israr[13], Muhammad Suhaib Qudus[14], Rabia Zahir[15], Waqas Khan[16], Zia Ul-Haq[17]

ABSTRACT

Objective: To analyze the clinical and histopathologic parameters of patients with breast cancer from the North West population of Pakistan.

Study Design: Cross sectional descriptive study.

Place and Duration of Study: Data was extracted from the Institute of Radiology and Nuclear Medicine Hospital, Peshawar and Khyber Teaching Hospital, Peshawar from March 2014 to December 2016.

Materials and Methods: Demographic, clinical and histopathological data was extracted from patient files using proformas. The following parameters were assessed: age, family history, marital status, side and type of surgery, resection margins, tumor markers, foci, tumor grade, TNM stage and lymph node, vascular and lymphatic invasion. Data was analyzed for descriptive statistics. Logistic regression was performed by stratifying patients according to the disease stage as early stage (ES) (stage I and II) and late stage (LS) (stage III and IV) to get odds ratios (ORs) and P -values.

Results: Clinical and histopathological data of 362 patients with breast cancer was profiled. From the available data 82 (33%) patients were early stage breast cancer, while 167 (67%) were late stage breast cancer. The mean age of patients in the ES breast cancer (45.8 years) was not statistically different from LS breast cancer (45.8 years) (p=0.99).

ER+ cases were 62%, PR+ cases were 47% and HER2 positive cases were 49%. Lymph node invasion (p<0.0001), vascular invasion (p=0.05) and lymphatic invasion (0.009) were statistically significantly associated with LS disease. Lymph node invasion was predictive of LS breast cancer (OR=17.1, p<0.0001). In addition, lymphatic invasion was predictive of LS breast cancer (OR=3.2, p=0.01).

Conclusion: The clinical and histopathologic patterns in ES and LS breast cancer are different which may require different management approaches. Majority of the patients present with late stage disease. Tumor markers positivity pattern differs from western population. Lymph node invasion is a better predictor of late stage disease.

Key Words: *Breast Cancer, Clinico-pathologic, Estrogen Receptors, HER2-Neu Peptide, Lymph Nodes, Progesterone Receptor.*

Introduction

Breast cancer is a commonly diagnosed female malignancy. In 2016, the estimated new cases of breast cancer were 249,260 with estimated deaths of 40,890 in USA.[1] It is estimated that one out of every nine women in Pakistan has a lifetime risk of developing breast cancer.[2,3] Pakistan has the highest burden of breast cancer in Asia and the disease manifest at a younger age and late stage with a poor prognosis.[3-6]

The epidemiological data from Pakistan is very limited due to lack of a national cancer registry.[7,8] However, the risk factors for developing breast cancer in Pakistan are female gender, age, socioeconomic status, family history, obesity, lack of physical activity, reduced breast feeding habit and hormonal factors like early menarche and delayed parity.[2,3,5,7] There is no implemented breast cancer-screening program in Pakistan and mammography is rarely used as a screening tool even among the educated women.[4,5,9] Clearly, this precludes early diagnosis of breast cancer and the disease presents at a late stage with high probability of metastatic or micro-metastatic disease.[10]

Apart from clinical and other histopathological variables used in the assessment of breast cancer,

[1,11,12,13,14,15,16]*Department of Histopathology*
Institute of Basic Medical Sciences
Khyber Medical University, Peshawar
Wolfson Wohl Cancer Research Center
Institute of Cancer Sciences
University of Glasgow, United Kingdom
[2,7]*Department of Surgery*
Medical Teaching Institute
Hayatabad Medical Complex, Peshawar
[3,6]*Department of Oncology*
Institute of Radiology and Nuclear Medicine
Peshawar

[4]*Department of Medicine*
Gajju Khan Medical College
District Hospital, Swabi
5Department of Surgery
Medical Teaching Institute
Khyber Teaching Hospital, Peshawar
[8,17]*Department of Pathology*
Rehman College of Rehabilitation Sciences
Peshawar
[9]*Department of Pathology*
Northwest Institute of Health Sciences, Peshawar
[10]*Department of Public Health*
Institute of Public Health and Social Sciences
Khyber Medical University, Peshawar

Correspondence:
Dr. Asif Ali
Assistant Professor, Histopathology
Institute of Basic Medical Sciences
Khyber Medical University, Peshawar
Wolfson Wohl Cancer Research Center
Institute of Cancer Sciences
University of Glasgow, United Kingdom
E-mail: draliasif7@gmail.com

Funding Source: NIL; Conflict of Interest: NIL
Received: July 05, 2017; Revised: Sep 28, 2017
Accepted: Nov 24, 2017

three tumor markers are also used namely: estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). These markers are used as prognostic and predictive factors in breast cancer.[9,11,12] ER, PR and HER2 are a routine diagnostic work-up in patients with breast cancer in Pakistan.

Breast cancer presentation patterns and histopathology findings vary in different regions and races.[1,13-16] Studies in Pakistan have attempted in analyzing the clinico-pathologic data[4,5] but they have not stratified breast cancer into different ethnicities. We plan to specifically to analyze the clinico-pathologic parameters and tumor marker status from northwest ethnic population of Pakistan. Analyzing the clinico-pathological data will help us in assessing the disease patterns and in clinical and public health intervention measures. The purpose of current study was to analyze the clinical and histopathological parameters of patients with breast cancer from the northwest population of Pakistan.

Materials and Methods

The current study was a cross sectional study. Data was extracted from the Institute of Radiology and Nuclear Medicine Hospital, Peshawar and Khyber Teaching Hospital, Peshawar from March 2014 to December 2016. The sample size of the current study was 362 patients with breast cancer and the sampling technique was consecutive sampling. The study was approved from the Ethics Board of Khyber Medical University, Peshawar.

The inclusion criteria were all the available clinical and pathological data for patients with breast cancer from March 2014 to December 2016 registered at Institute of Radiology and Nuclear Medicine Hospital, Peshawar with the availability of data for these patients in Khyber Teaching Hospital, Peshawar. Thus, this data represents the northwest Pakistani population as patients from every district come to these hospitals for breast cancer treatment. The exclusion criteria were patients with metastatic disease to breast, other breast tumors, secondary tumors in breast and recurrent breast cancer.

A data collection instrument was developed with the help from pathologists and oncologists and was used to catalogue the data. Demographic, clinical and histopathological data was extracted for patients with breast cancer. The demographic and clinical data included age of the patient, marital status, family history of breast cancer and surgical information (laterality of tumor and type of surgery). The histopathological data included lymph node invasion, vascular invasion, lymphatic invasion, grade of the tumor, TNM stage of the tumor, resection margin status and final diagnosis and subtypes of breast cancer. In addition, data on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status was retrieved from patient files.

Data was analyzed for descriptive statistics. The distribution of data was assessed using Histogram with normal curve. Based on the presentation of data independent sample t test was used for comparing the means between the two groups (group 1=age in early stage breast cancer; group 2=age in late stage breast cancer). In addition, Fisher's exact test or chi square test was used for categorical data depending on the number of data points in the cells of a 2×2 table and sample size assumption. Logistic regression was performed by stratifying patients according to the disease stage as early stage (stage I and II, ES) and late stage (stage III and IV, LS) to get odds ratios (ORs) and P -values. P value ≤ 0.05 was considered statistically significant. SPSS version 21 was used for all statistical analyses.

Results

Clinical and pathological data of 362 patients with breast cancer was profiled. The mean ± standard deviation age of patients with breast cancer was 45.7 ± 11.9 years. The age of patients with breast cancer follow a normal distribution.

The mean age of patients in the early stage breast cancer (45.8 years) was not statistically different than the mean age of patients with late stage breast

cancer (45.8 years) (p=0.99, independent sample t test) (Table 1).

From the available data 82 (33%) patients were early stage breast cancer, while 167 (67%) were late stage breast cancer. Moreover, the histologic subtypes were ductal (88%), medullary (5%), lobular (4%) and other types (3%). ER+ cases were 62%, PR+ cases were 47% and HER2 positive cases were 49%.

The other clinical and pathological variables including family history, marital status, laterality of tumour, lymph node status, vascular invasion, lymphatic invasion, resection margin status, ER status, PR status, HER2 status, tumour grade, type of surgery and tumour foci were cross tabulated with disease stage (ES breast cancer and LS breast cancer) to identify any relationship.

Lymph node invasion (p<0.0001, Fishers' Exact test), vascular invasion (p=0.05, Chi Square test and lymphatic invasion (0.009, Chi Square test) were statistically significantly associated with late stage disease. In addition, HER2 positivity and type of surgery (modified or total mastectomy) were also associated with late stage disease with a trend towards statistical significance (p=0.07 and p=0.08 respectively, Chi Square test).

Next, we assessed the predictive significance of clinical and pathological variables using logistic regression model. On univariate logistic regression lymph node invasion was predictive of late stage breast cancer (OR=17.1, 95% CI 4.36-66.9, p<0.0001). In addition, lymphatic invasion was predictive of late stage breast cancer (OR=3.2, 95% CI 1.32-8.06, p=0.01). Finally, there was a trend towards statistical significance in case of vascular invasion and ER positivity for predicting late stage breast cancer (p=0.07 and p=0.09 respectively).

Discussion

The current study compiled and analysed the clinico-pathologic data of 362 patients with breast cancer. The available data was entered into different statistical models to explain clinically relevant information for pathologists, oncologists and surgeons. This study specifically reported the clinico-pathologic characteristics of patients with breast cancer from the northwest Pakistani population.

The mean age of patients diagnosed with breast cancer is similar to the African population.[13] There was no difference in the mean age of patients with early stage breast cancer and late stage breast cancer in the current study. The median age of patients diagnosed with breast cancer in Pakistani population is very low (45 years) compared to USA population (62 years).[1,16,17] In addition, less than 5% of the cases presents with age less than 40 years in USA.[1,17,18] However, in our study 26% of the patients presented with age less than 40 years. Furthermore, there is no difference in the mean age of patients in early stage and late stage breast cancer in our population but patients in late stage disease are 4 years older in African population.[13] These figures in our study compared to the published literature are alarming and require public health intervention measures.

Majority of patients present at a late stage (67%) in Pakistani population compared to Brazil (53%)[4] and Egypt (46%).[19] Interestingly, in USA only 17% of the cases of breast cancer are diagnosed at a later stage.[15] The difference between Pakistan and USA (67% versus 17%) is striking. The early diagnosis of breast cancer in USA is attributed to the fact that the breast screening and its awareness is a routine practice in USA.[15,20] Thus, this mandates the need for early diagnosis through the introduction of mammography as a screening tool in Pakistan with properly planned breast cancer awareness campaigns.

The histologic subtypes presented in the current study are significantly different from the reported literature.[2,21] This may be, because, patients who visit the hospitals included in the study might have previous pathology reports from a variety of different pathology laboratories. Logistically, validating all the reports from different laboratories is a challenging task which might be difficult to achieve in resource limited settings.

Furthermore, the rates of ER, PR and HER2 positivity in Pakistani population appear different. ER+ cases a significantly less (62%) compared to western population (78%) and PR+ cases are, again significantly less (47%) compared to western population (60%). In contrast, HER+ cases are more than 2 times higher in Pakistani population compared to western population.[11,12] The under-reporting of ER and PR and over-reporting of HER2 may have attributed to the fact that the immunohistochemistry protocols and the reporting criteria might not be stringent in pathology labs of Pakistan. This warrants a standardised immunohistochemistry protocol, a standardised and validated scoring criterion and a validated diagnostic cut-off.[5]

Moreover, we assessed the utility of various clinical and pathological variables for any association and or prediction of late stage breast cancer. Lymph node invasion, vascular invasion and lymphatic invasions were associated with late stage disease. These findings support the existing literature.[22]

HER2 positive cases are present mostly in late stage breast cancer and again this finding supports the

existing literature.[9,22] Modified radical and or total mastectomy are offered as a treatment option to patients with late stage breast cancer. However, the current literature suggests that breast conserving surgery could potentially be an option in stage III disease.[23] Thus, these findings suggest that the surgical practice could potentially become more rigorous and may move toward breast conserving surgery.

Finally, lymph node invasion and lymphatic invasion as predictor or explanatory variables could predict late stage disease as a predicted or response variable. These findings are consistent with the existing literature.[4,14,15,19] These predictive factors should thus be considered in the pathology reports as a "marker" of late stage disease.

Conclusion

The clinico-pathologic patterns in early stage and late stage breast cancer are different, which may require different management approaches. Majority of the patients present with late stage disease, however, age at presentation is similar in early stage and late stage disease. Tumor markers positivity pattern differs from western population which may require further studies to identify the risk factors. Lymph node invasion is a better predictor of late stage disease and may be used as a surrogate marker of late stage presentation.

Analysis of the clinico-pathologic parameters could have important clinical and public health applications. We hope that these findings from a relatively large sample of patients would help to improve the management of patients with breast cancer in our local population.

Table I: The Distribution of Age in Early Stage and Late Stage Breast Cancer

Group Statistics						*P* value*
	Grouping ES, LS	N (%)	Mean	Std. Deviation	Std. Error Mean	
Age	ES	82 (23%)	45.87	11.356	1.254	0.99
	LS	167 (77%)	45.86	12.197	.944	

Abbreviations: ES= Early stage breast cancer, LS=Late stage breast cancer

*Independent sample t test

Table II: Cross Tabulation (Chi Square Test and Fisher's Exact Test) of Clinical and Pathological Variables with Disease Stage

Variables	Early Stage Breast Can cer (Stage 1 & 2)	Late Stage Breast Cancer (Stage 3 & 4)	*P* value
Family History No Yes	 48 4	 106 7	0.46[b]
Marital Status Married Unmarried	 58 5	 121 14	0.58[a]
Laterality of Tumour Left Right NA Bilateral	 16 19 43 0	 37 42 72 0	0.56[a]
Lymph Node Invasion Absent Present	 10 23	 3 118	0.000[b]
Vascular Invasion Absent Present	 12 09	 8 20	0.05[a]
Lymphatic Invasion Absent Present	 27 10	 24 29	0.009[a]
Resection Margin R0 R1	 15 17	 30 17	0.13[a]
ER Status Absent Present	 16 33	 34 51	0.10[a]
PR Status Absent Present	 20 25	 40 35	0.12[a]
HER2 Status Absent Present	 19 19	 12 25	0.07[a]
Tumour grade I and II III	 33 49	 38 77	0.29[a]
Type of Surgery Lumpectomy Modified/Total Mastectomy	 23 21	 28 48	0.08[a]
Tumour Foci Focal Lesions Multiple Lesions	 22 10	 43 10	0.19[a]

Abbreviations: a = Chi Square Test, b = Fisher's Exact Test, R0 = Negative resection margin, R1 = Positive resection margin, ER = Oestrogen receptor, PR = Progesterone receptor, HER2 = Human epidermal growth receptor

Table III: Logistic Regression Modelling to Assess the Predictive Significance of Clinico-Pathological Variables for Late Stage Disease

Variables	Odds Ratio	95% CI	*P* value
Positive family history	0.79	0.22-2.83	0.72

Married	1.34	0.46-3.90	0.58
Laterality of tumour	0.83	0.59-1.18	0.31
Lymph node invasion	17.1	4.36-66.9	0.000
Vascular invasion	3.00	0.91-9.96	0.07
Lymphatic invasion	3.26	1.32-8.06	0.01
Resection margin positivity	0.50	0.20-1,24	0.13
ER Positivity	0.56	0.30-1.10	0.09
PR Positivity	0.58	0.29-1.17	0.13
HER2 Positivity	1.32	0.57-3.03	0.50
High Tumour grade	1.36	0.75-2.45	0.30
Mastectomy (Radical/Total)	1.87	0.88-3.98	0.10
Multiple tumour foci	0.51	0.18-1.41	0.19

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: A Cancer Journal for Clinicians. 2016; 66: 7-30.
2. Malhotra GK, Zhao X, Band H, Band V. Histological, molecular and functional subtypes of breast cancers. Cancer Biology & Therapy. 2010; 10: 955-60.
3. Menhas R, Umer S. Breast Cancer among Pakistani Women. Iranian Journal of Public Health. 2015; 44: 586-7.
4. Badar F, Mahmood S, Faraz R, Quader AU, Asif H, Yousaf A. Epidemiology of Breast Cancer at the Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2015; 25: 738-42.
5. Basra MA, Saher M, Athar MM, Raza MH. Breast Cancer in Pakistan a Critical Appraisal of the Situation Regarding Female Health and Where the Nation Stands? Asian Pacific journal of cancer prevention : APJCP. 2016; 17: 3035-41.
6. Badar F, Mahmood S. Hospital-based cancer profile at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, pakistan. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2015; 25: 259-63.
7. Asif HM, Sultana S, Akhtar N, Rehman JU, Rehman RU. Prevalence, risk factors and disease knowledge of breast cancer in Pakistan. Asian Pacific journal of cancer prevention : APJCP. 2014; 15: 4411-6.
8. Sufian SN, Masroor I, Mirza W, Butt S, Afzal S, Sajjad Z. Evaluation of Common Risk Factors for Breast Carcinoma in Females: a Hospital Based Study in Karachi, Pakistan. Asian Pacific journal of cancer prevention : APJCP. 2015; 16: 6347-52.
9. Sohail S, Alam SN. Breast cancer in pakistan - awareness and early detection. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2007; 17: 711-2.
10. Screening mammography for women aged 40 to 49 years at average risk for breast cancer: an evidence-based analysis. Ontario health technology assessment series. 2007; 7: 1-32.
11. Kinsella MD, Nassar A, Siddiqui MT, Cohen C. Estrogen receptor (ER), progesterone receptor (PR), and HER2 expression pre- and post- neoadjuvant chemotherapy in primary breast carcinoma: a single institutional experience. International journal of clinical and experimental pathology. 2012; 5: 530-6.
12. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clinical medicine & research. 2009; 7: 4-13.
13. Burson AM, Soliman AS, Ngoma TA, Mwaiselage J, Ogweyo P, Eissa MS, et al. Clinical and Epidemiologic Profile of Breast Cancer in Tanzania. Breast disease. 2010; 31: 33-41.
14. Hunter CP. Epidemiology, stage at diagnosis, and tumor biology of breast carcinoma in multiracial and multiethnic populations. Cancer. 2000; 88: 1193-202.
15. Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. Jama. 2015; 313: 165-73.
16. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, et al. Trends in breast cancer by race and ethnicity: update 2006. CA Cancer J Clin. 2006; 56: 168-83.
17. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin. 2014; 64: 5262.
18. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Annals of internal medicine. 2012; 156: 635-48.
19. Stapleton JM, Mullan PB, Dey S, Hablas A, Gaafar R, Seifeldin IA, et al. Patient-mediated factors predicting early- and late-stage presentation of breast cancer in Egypt. Psycho-oncology. 2011; 20: 532-7.
20. Matsen CB, Neumayer LA. Breast cancer: a review for the general surgeon. JAMA surgery. 2013; 148: 971-9.
21. Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. Clinical Medicine Insights Pathology. 2015; 8: 23-31.
22. Verma R, Bowen RL, Slater SE, Mihaimeed F, Jones JL. Pathological and epidemiological factors associated with advanced stage at diagnosis of breast cancer. British medical bulletin. 2012; 103: 129-45.
23. Chagpar AB, Killelea BK, Tsangaris TN, Butler M, Stavris K, Li F, et al. A Randomized, Controlled Trial of Cavity Shave Margins in Breast Cancer. New England Journal of Medicine. 2015; 373: 50310