

Morphologic Spectrum of Breast Carcinoma and Correlation of Hormone Receptors and Her2/Neu Status with Clinic-Pathologic Parameters at a Tertiary Care Hospital

MARIA TASNEEM KHATTAK¹, MASROOR HASSAN², SARAH JAVED³, SHAHID HASNAIN⁴, RAAZIA MAHMOOD⁵, AMBREEN ALI⁶

¹Assistant Professor, Department of Pathology, Rehman Medical Institute/Rehman College of Dentistry, Peshawar

²Assistant professor, Department of Pathology, Northwest General Hospital and Research Center/Northwest School of Medicine, Peshawar

^{3,4,5}Trainee medical officer, Department of pathology, Rehman Medical Institute, Peshawar

⁶Associate Prof, Department of Pathology, Pak International Medical College, Peshawar

Corresponding author: Masroor Hassan, Cell: 0336-9192387

ABSTRACT

Background: After cardiovascular problems, cancer is the 2nd biggest cause of mortality globally. Globally, breast cancer is recognized as the second most prevalent cancer in general, the most prevalent cancer in women, and the 5th major cause of cancer-related death.

Objectives: To study the Morphologic Spectrum of Breast Carcinoma and correlation of hormone receptors and HER2/neu status with clinic-pathologic parameters

Methods: A total of 97 consecutive cases of modified radical mastectomy were evaluated in the department of histopathology, Rehman Medical Institute Peshawar from February 2019 to December 2020. Expression of PR, ER and Her2/neu were scored similar to College of American Pathologist's (CAP) guidelines. The analysis of data was done by using SPSS version.

Results: Mean age of presentation was 49.6 years. The most prevalent histological subtype was invasive carcinoma of no particular type (72.2%). Grade II tumors were most frequent (43.3%). Lymphovascular and perineural invasion were present in 53.6% and 40.2% of cases respectively. Pathologic stage pT2 was most frequent (56.7%). Macrometastasis was noted in 61.8% of cases. ER and PR showed positivity in 59.8% and 51.5% of cases and Her2/neu was over expressed in 30.9% of cases. ER positivity inversely correlated with Her2/neu but directly with tumor size. Strong association was found between ER/PR positivity and HER2/neu with histologic grade.

Conclusion: Our study showed a diverse spectrum of special type carcinomas, none of which showed HER2/neu over expression. Majority of our patients belong to a younger age group and presented with advanced disease. Triple negative breast cancer (TNBC) was commonest in our population after luminal A. HER2/neu overexpression was limited to grade 2 and 3 of invasive ductal carcinoma

Keywords: Morphologic Spectrum; Breast Carcinoma; Hormone receptors

INTRODUCTION

After cardiovascular problems, cancer is the 2nd biggest cause of mortality globally.¹ Globally, breast cancer is recognized as the second most prevalent cancer in general, the most prevalent cancer in women, and the 5th major cause of cancer-related death.² However in women, it is the commonest cause of cancer related death in less developed regions and ranks 2nd in more developed countries.² Breast cancer together with lung, colorectal, prostate, stomach and liver cancers contribute more than half of total cancer incidence.²

Because of lack of national cancer registry in Pakistan, we have no national data regarding the prevalence of various malignancies, rather studies provide variable regional data because of different ethnic composition.³ Although there are significant differences in prevalence in different regions of Pakistan, breast cancer still ranks 1st as the commonest cancer in women.³ Pakistan has highest incidence of breast cancer in Asia, about 2.5 times that of its neighboring countries, India and Iran.⁴ In Pakistan, compared to the western countries, breast cancer is diagnosed a decade earlier (i.e. 4th decade) and mostly at higher stage, thus suggesting earlier screening.^{5,6}

In our province of Khyber Pakhtunkhwa, more than 60% of breast cancer patients present with an advanced disease (stage III or IV) due to lack of awareness, financial problems, difficulty to access healthcare facility, undue reassurance, old age, breast lump being painless or other associated comorbidities etc.⁷ The prognosis of breast cancer not only depends on early diagnosis and prompt treatment but also on regional nodal metastasis, distant metastasis, tumor size, lymphovascular invasion, histologic and molecular subtype, histologic grade, proliferative index, hormone receptor and HER2/neu expression status.^{8,9,10}

The positivity of the receptor of estrogen and progesterone and Her2/neu expression status detected by immunohistochemistry (IHC) have important role in breast cancer management as their expression is correlated with different prognostic parameters.¹¹ Tamoxifen is a therapeutic hormone that

blocks estrogen receptors on breast cancer cells and is used to treat ER positive breast cancers.¹¹ Similarly PR has importance in predicting the behavior of breast carcinoma as its loss of expression by IHC is associated with poor prognosis.¹² Proliferation of cells and suppression of apoptosis is done by a proto-oncogene called human epidermal growth factor receptor 2.^{13,14} It is expressed in a variety of malignancies including breast carcinoma, pulmonary, prostatic, colorectal and gastric adenocarcinoma, squamous cell carcinoma of lung, and urothelial carcinoma of urinary bladder.¹⁴ Its over-expression predicts tumor response to trastuzumab and poor overall survival.¹¹

To sum up, our present study is directed to highlight the histologic spectrum of different types of breast carcinoma in our tertiary care setup, its clinic-pathological features and correlation with hormone receptors and Her2/neu expression status.

METHODOLOGY

This study was descriptive, cross-sectional piloted at Histopathology department of Rehman Medical Institute (RMI), Peshawar from November 1st 2019 to 31st December 2020. Proper approval was taken from Institutional Committee of Research and Ethics. All consecutive breast carcinoma cases, whether in-house or referred from other centers were included in the study. Only those patients who underwent modified radical mastectomy were included while incisional biopsies, core biopsies and excisional biopsies / simple mastectomies without lymph node dissection were excluded. Only carcinomas were included while cases of malignant phyllodes, primary breast sarcomas, lymphomas and metastatic tumors were excluded. Mastectomies having ductal carcinoma in situ only were also excluded. Similarly recurrent cases were also excluded. College of American Pathologists (CAP) guidelines were used according to the previous study.¹⁵ Haematoxylin and eosin was used to stain 4 micrometer sections of formalin-fixed and paraffin-embedded blocks of tissues for light microscopy. CAP guidelines were used for reporting.¹⁵ The Elston-Ellis modification of the

Scarff-Bloom-Richardson grading system was used to grade malignancies histologically.¹⁵ Tumor size was divided into three categories i.e. ≤ 2 cm, >2 to ≤ 5 cm and > 5 cm. FFPE tissue blocks were utilized to find out ER, PR while HER2/neu position by using polyclonal rabbit anti-human antibody (Dako) and clone ID5 (DAKO), IA6 (DAKO) respectively. External control for HER2/neu was an FFPE block of a known breast cancer with strong positive HER2/neu, whereas internal control for ER and PR was a normal breast lobule adjacent to the tumor. Hormone receptors and HER2/neu expression was scored by two pathologists. Assessment of hormone receptors was based on staining intensity and percentage of positive cells using Allred scoring system. ER and PR were graded positive when nuclear staining was shown by more than 1% of malignant cells (i.e. a total score of 3 or more). For HER2 over expression, tumors with IHC values of zero or 1+ were declared negative, while tumors with 3+ were classified positive. 2+ IHC score was measured equivocal which was not further evaluated by Fluorescent in situ hybridization (FISH) due to the lack of facility. Breast cancer was classified based on IHC expression of ER, PR and HER2/neu into four main receptor-defined surrogate subtypes: 1. ER/PR Positive, HER2 Negative (Luminal A), 2. ER/PR Positive, HER2 Positive (Luminal B / Triple Positive), 3. ER/PR Negative, HER2 Positive (HER2 Enriched), 4. ER/PR Negative, HER2 Negative (Triple Negative). For continuous variables like age, mean \pm standard deviation was calculated. For categorical variables, frequency and percentage were calculated. SPSS-23 was used for statistical analysis. For determination of association between ER, PR and HER2/neu overexpression with clinicopathological parameters, Chi square test was applied. A probability p value of <0.05 was considered statistically significant.

RESULTS

Ninety-seven cases of breast carcinoma were included in the study, all of which were females. The mean age was 49.6 years \pm 13.81 SD (range 24-85 years; median age 47 years). More than half of the patients (n=52, 53.6%) were diagnosed before 50 years, of which half of the patients (n=27, 50.9%) were in 4th decade. The tumors predominantly involved left breast (n=58, 59.8%) and upper-outer quadrant was the most common location (n=44, 45.4%). Majority (n=89, 91.8%) of the tumors were unifocal. The most common histologic type was invasive carcinoma of no special type (invasive ductal carcinoma) (n=70, 72.2%), followed by 10 cases (10.3%) of invasive lobular carcinoma, 5 cases (5.2%) of invasive carcinoma with medullary features, 4 (4.1%) cases of mucinous carcinoma, 3 (3.1%) cases of metaplastic carcinoma and 1 (1%) case each of micropapillary carcinoma, secretory carcinoma, tubular carcinoma, solid papillary carcinoma with invasion and cribriform carcinoma, NOS. Figure 1.

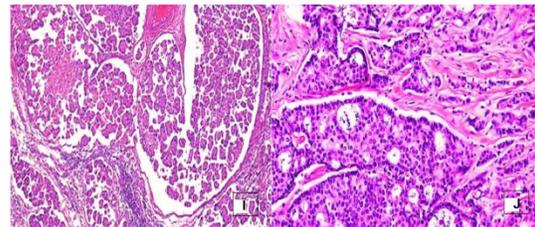
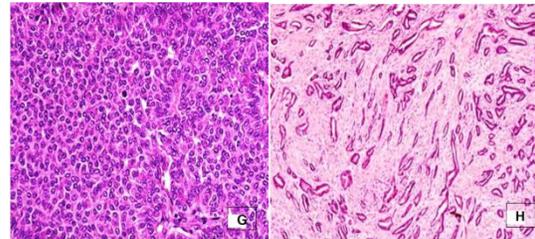
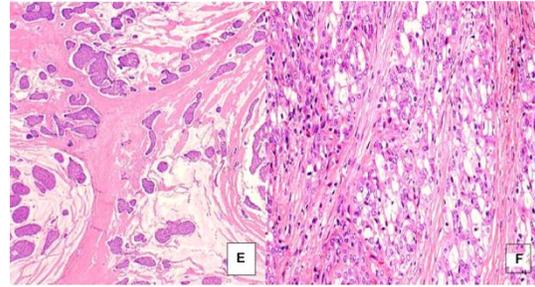
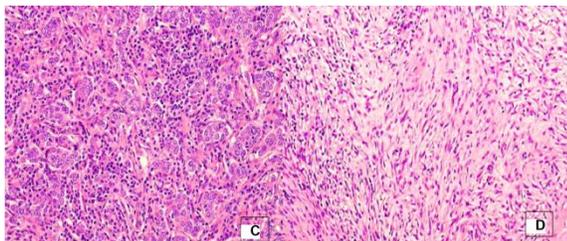
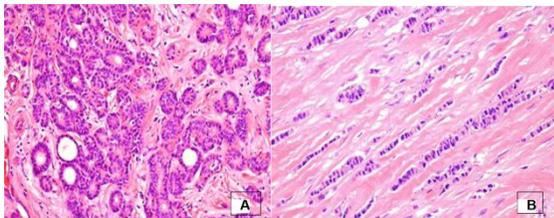


Figure 1: Hematoxylin and eosin stained sections at 10x magnification showing a) invasive ductal carcinoma, b) invasive lobular carcinoma, c) invasive carcinoma with medullary features, d) metaplastic carcinoma, e) mucinous carcinoma, f) secretory carcinoma, g) solid papillary carcinoma, h) tubular carcinoma, i) micropapillary carcinoma, j) cribriform carcinoma.

Tumor size ranged from 0.2 cm to 9.3 cm. Most (n=61, 62.9%) of the tumors were in size range of 2-5 cm. Ductal carcinoma in situ was associated with 59 cases (60.8%). Grade II tumors were the commonest (n=42, 43.3%), followed by grade III (n=34, 35.1%). Fifty-two cases (53.6%) showed lymphovascular invasion (LVI) while perineural invasion (PNI) was present in 39 cases (40.2%). Pathologic stage pT2 was most frequent (n=55, 56.7%) followed by pT1c (n=26, 26.8%). Thirty-two cases (33%) had no regional metastasis while 5 (5.2%) had micrometastasis and rest (n=60, 61.8%) had macrometastasis. Regarding hormone receptors, 58 cases (59.8%) expressed ER and 50 cases (51.5%) were positive for PR. Thirty cases (30.9%) strongly expressed (3+) Her2/neu, 54 cases (55.7%) were negative (0 and 1+) and 13 cases (13.4%) were equivocal (2+). Luminal A was the commonest receptor defined surrogate subtype (n=35, 36.1%) followed by TNBC (n=19, 19.1%). In 13 cases, further subtyping was not possible due to equivocal HER2/neu. Strong linkage was observed between HER2/neu enriched and TNBC with grade III (p <0.001). ER positivity inversely correlated with Her2/neu over expression (p=0.03), while no association was found between PR positivity and HER2/neu expression (p=0.3). Strong association was found between hormone positivity and histologic grade (p <0.001 for ER and p=0.001 for PR). Hormone positivity was also associated with tumor size (p=0.04 for ER and 0.01 for PR). Similarly Her2/neu overexpression was also strongly associated with tumor grade (p=0.02). Her2/neu overexpression was more common in left sided tumors (22 out of 30 cases). No correlation was found between ER, PR and HER 2/neu with age, LVI, PNI, nodal metastasis and pathologic stage. Also there was no association of HER2/neu with tumor size. Table 1

Table 1: Correlation of estrogen, progesterone and Her2/neu with clinicopathological parameters

	Estrogen (p value)	Progesterone (p value)	Her2/neu (p value)
Age	0.38	0.74	0.1
Histologic grade	<0.001	0.001	0.02
Tumor size	0.047	0.01	0.1
Lymphovascular invasion	0.089	0.12	0.85
Perineural invasion	0.89	0.96	0.28
Pathologic pT stage	0.13	0.07	0.27
Nodal metastasis	0.27	0.18	0.5

DISCUSSION

Mean age of presentation was 49.6 years in patients included in our study. Left breast was more commonly involved (59.8%), most prevalent histological subtype was invasive carcinoma of no particular type (72.2%), grade II was the commonest histologic grade (43.3%) and 61.8% had nodal macrometastasis. All these findings are similar to another national study conducted in southern region in which mean age was 48.3 years, 66% of cases presented before 50 years, 57% involved left breast, most prevalent histological subtype was invasive carcinoma of no particular type (85.3%) and the most frequent grade was grade II (55.3%).¹¹ Similarly in another national study by Bhurgri et al, 60% patients presented before 50 years of age, 59% had grade II, 56% had nodal metastasis and left breast was more commonly involved.¹⁶ Study from Shaikat Khanum Memorial Cancer Hospital and Research center (SKMCH and RC) also showed comparable results, however most of the tumors were grade III (49.6%).⁶ It is estimated that relative to 2015, breast malignancies in women of age 30-34 will increase to 130.6% by 2025.¹⁷

Our study showed a diverse spectrum of special type carcinomas including mucinous carcinoma, metaplastic carcinoma, tubular carcinoma, cribriform carcinoma, invasive carcinoma with medullary features, secretory carcinoma and solid papillary carcinoma, none of which showed HER2/neu over expression, a finding which is supported by national and international studies.^{11,18} Similarly none of classic invasive lobular carcinoma were HER2/neu positive as observed in another study.¹⁸ In our study HER2/neu overexpression was strongly associated ($p=0.02$) with higher grade tumors and all of the grade I tumors were HER2/neu negative which is in accordance to the study conducted in Karachi, New York and Ivory Coast.^{11,18,19}

Due to biological heterogeneity of breast carcinoma, various clinicopathological factors determine prognosis and response to therapy including histological type of carcinoma, tumor grade and size, vascular invasion, nodal metastasis, hormone receptor expression, Her2/neu status, stage and age of the patient.²⁰ Similarly hormone receptors and HER2/neu expression shows marked variability in expression regarding geographic distribution and ethnicity. In our study, 59.8% of cases were positive for ER, 51.5% for PR and 30.9% cases showed HER2/neu over expression which is similar to the study by Gogia et al showing 59% ER positivity and 29% HER2/neu positivity.²¹ A national study by SKMCH and RC showed ER positivity in 62%, PR 50.3% and HER2/neu in 24.6% of cases.⁶ Similarly a large comparative retrospective study among Iraqi and British women showed ER, PR and HER2/neu positivity in 69.2%, 66.7% and 29.2% of Iraqi women however the British women showed higher ER (86.5%) and PR (79.7%) positivity and lower HER2/neu (12.6%) expression.²² Our frequency of hormonal expression is also supported by another study from our northern region showing 62.2% and 60.1% positivity of ER and PR, however their HER2/neu overexpression was slightly more (38.9%).²³

Our study showed luminal A in 36.1%, luminal B in 12.4%, HER2 enriched in 18.6% and TNBC in 19.6% of cases. An observational study from SKMCH and RC showed comparable results with 37.3%, 13.7%, 10.9% and 16.6% cases of luminal A, luminal B, Her2 enriched and TNBC.⁶ A study by Alwan et al shows 47.4%, 13.7%, 10.7 and 14.7% of luminal A, luminal B,

HER2 enriched and TNBC cases respectively in Iraqi women while comparative British women in similar study showed 73.3%, 7%, 2.5% and 5% cases of luminal A, luminal B, HER2 enriched and TNBC.²² This concludes that developed western societies are more likely to be ER+/HER2- and hence luminal A as compared to the developing countries.²² Similarly in another study luminal A was found in 58.5% of cases, luminal B in 14%, HER2 enriched in 11.5% and TNBC in 16% of cases.²⁴ Moreover as the histologic grade of tumor increased in our study, the proportion of TNBC also increases from 10% to 26% to 63% in grade I, II and III respectively ($p<0.001$) similar to other international studies.²⁴⁻²⁶

In our study, ER ($p<0.001$), PR ($p=0.001$) and HER2/neu ($p=0.02$) expression shows strong correlation with tumor grade. Similarly overexpression of Her2/neu inversely correlated with ER expression ($p=0.03$) which is similar to other national and international studies.^{11, 18, 20, 23, 25, 27,28} Moreover hormone receptors also showed correlation with tumor size ($p=0.04$ for ER, $p=0.01$ for PR). Hormone receptors also strongly correlated with size in other studies however they found no association between HER2/neu and tumor size.^{23, 27}

In a study by Luangxay et al, majority of tumors presented with pT2 (60.2%), followed by pT3 (25.0%) and pT4 (7.9%).²⁶ Similarly in our study, 56.7% of cases presented in pT2 and 6.2% cases in pT3. In a large study ($n=1358$) conducted in Khyber Pakhtunkhwa from 2006- 2008, most of the patients presented with pathologic stage pT3 (42.45%), histologic grade II (45.4%) and in 5th decade (31.1%).²⁹ However, in our study, diagnosis at an earlier age with lower pathologic stage and histologic grade in similar region may reflect early referral to health facilities and timely diagnosis and treatment. Our study do not show any significant correlation of hormone receptors and HER2/neu with age, vascular and perineural invasion, regional nodal metastasis and pathological stage which is in line with other studies.^{11, 20}

As our study is predominantly hospital based, so it may not represent the underlying general population of the region, as we received patients from Afghanistan as well, highlighting the lack of population based sampling. Due to unavailability of facility, cases having equivocal HER2/neu were not subjected to FISH analysis for exact HER2 status. Similarly due to lack of Ki-67, CK5/6 IHC markers and FISH for HER2/neu 2+ cases, we couldn't fully classify the tumors into receptor-defined surrogate subtypes.

CONCLUSION

A variety of different histologic types of breast carcinoma were observed. Majority of our patients belong to a younger age group and presented with lower pathologic stage. TNBC was more common in our population after luminal A breast cancer. Expression of ER was directly related with PR and reciprocally associated with Her2/neu. Similarly HER2/neu overexpression was limited to grade 2 and 3 of invasive ductal carcinoma. Strong linkage was observed between HER2/neu enriched and TNBC with grade III tumors. By collecting a quality data from patients, this descriptive study will be helpful in monitoring the changing trends after new public health initiatives. In developing countries like ours, there is a need to increase awareness by educating public and hence timely detection and control of disease burden.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):359-86.
3. Idrees R, Fatima S, Abdul-Ghaffar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. *World J Surg Oncol.* 2018;16(1):129.
4. Begum N. Breast Cancer in Pakistan: A Looming Epidemic. *J Coll*

- Physicians Surg Pak. 2018;28(2):87-
5. Pakistan: An experience at a tertiary care center. *J Pak Med Assoc.* 2018;68(11):1682-85.
6. 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. *J Coll Physicians Surg Pak.* 2015;25(10):738-42.
7. Khan A, Khan K, Raza A, Din Qureshi ZU, Sultan B, Khan FA. Patient Self Delay Among Women With Breast Cancer. *J Ayub Med Coll Abbottabad.* 2018;30(4):558-61.
8. Lester SC. The Breast. In: Kumar V, Abbas AK, Aster JC. eds. *Robins and Cotran Pathologic basis of disease.* 9th edn Philadelphia: Elsevier, 2015:1066-68
9. Collins LC. Breast. In: Goldblum JR, Lamps LW, McKeeney JK, Myers JL. eds. *Rosai and Ackerman's Surgical Pathology.* 11th edn Philadelphia: Elsevier, 2018:1494-95
10. Yao C, Liu Y, Huang H, Zhang J. Correlation between clinicopathological features and postoperative prognosis in patients with breast cancer. *Int J Clin Exp Med* 2018;11(3):2483-88.
11. Azizun-Nisa, Bhurgri Y, Raza F, Kayani N. Comparison of ER, PR and HER-2/neu (C-erb B 2) reactivity pattern with histologic grade, tumor size and lymph node status in breast cancer. *Asian Pac J Cancer Prev.* 2008;9(4):553-56.
12. Collett K, Hartveit F, Skjaerven R, Maehle BO. Prognostic role of oestrogen and progesterone receptors in patients with breast cancer: relation to age and lymph node status. *J Clin Pathol.* 1996;49(11):920-5.
13. Ménard S, Casalini P, Campiglio M, Pupa SM, Tagliabue E. Role of HER2/neu in tumor progression and therapy. *Cell. Mol. Life Sci.* 2004;61:2965–78.
14. Koeppen HK, Wright BD, Burt AD, Quirke P, McNicol AM, Dybdal NO, et al. Overexpression of HER2/neu in solid tumours: an immunohistochemical survey. *Histopathology* 2001;38:96-104.
15. Fitzgibbons PL, Connolly JL, Bose S, Chen YY, de Baca ME, Edgerton M et al. Protocol for the Examination of Resection Specimens From Patients With Invasive Carcinoma of the Breast. [Online] 2020 [cited 2020 April 17].
16. Bhurgri Y, Kayani N, Faridi N, Pervez S, Usman A, Bhurgri H, et al. Pathoepidemiology of breast cancer in Karachi '1995-1997'. *Asian Pac J Cancer Prev.* 2007;8(2):215-20.
17. Zaheer S, Shah N, Maqbool SA, Soomro NM. Estimates of past and future time trends in age-specific breast cancer incidence among women in Karachi, Pakistan: 2004-2025. *BMC Public Health.* 2019;19(1):1001.
18. Lal P, Tan LK, Chen B. Correlation of HER-2 status with estrogen and progesterone receptors and histologic features in 3,655 invasive breast carcinomas. *Am J Clin Pathol.* 2005;123(4):541-6.
19. Aman NA, Doukoure B, Koffi KD, Kouli BS, Traore ZC, Kouyate M, et al. HER2 overexpression and correlation with other significant clinicopathologic parameters in Ivorian breast cancer women. *BMC Clin Pathol.* 2019;19:1
20. Azami A, Madani SH, Khazaei S, Izadi B, Saleh E, Sajadimajd S. Survey of low ERpositive expression and its correlation with other clinical and pathological factors in breast cancer. *Indian J Pathol Microbiol.* 2020;63, Suppl S1:129-33
21. Gogia A, Deo S V, Shukla N K, Mathur S, Sharma D N, Tiwari A. Clinicopathological profile of breast cancer: An institutional experience. *Indian J Cancer* 2018;55:210-13.
22. Alwan NAS, Kerr D, Al-Okati D, Pezella F, Tawfeeq FN. Comparative Study on the Clinicopathological Profiles of Breast Cancer Among Iraqi and British Patients. *The Open Public Health Journal.* 2018;11(1):177-91.
23. Faheem M, Mahmood H, Khurram M, Qasim U, Irfan J. Estrogen receptor, progesterone receptor, and Her 2 Neu positivity and its association with tumour characteristics and menopausal status in a breast cancer cohort from northern Pakistan. *Ecancermedalscience.* 2012;6:283.
24. Al-Thoubaity FK. Molecular classification of breast cancer: A retrospective cohort study. *Ann Med Surg.* 2019;49:44-8.
25. Bansal C, Sharma A, Pujani M, Pujani M, Sharma KL, Srivastava AN, Singh US. Correlation of Hormone Receptor and Human Epidermal Growth Factor Receptor2/neu Expression in Breast Cancer with Various Clinicopathologic Factors. *Indian J Med Paediatr Oncol.* 2017;38(4):483–89.
26. Luangxay T1,2, Virachith S, Hando K, Vilayvong S, Xaysomphet P, Arounlansy P, et al. Subtypes of Breast Cancer in Lao P.D.R.: A Study in a Limited-Resource Setting. *Asian Pac J Cancer Prev.* 2019;20(2):589-94.
27. Mwakigonja AR, Lushina NE, Mwanga A. Characterization of hormonal receptors and human epidermal growth factor receptor-2 in tissues of women with breast cancer at Muhimbili National Hospital, Dar es salaam, Tanzania. *Infect Agent Cancer.* 2017;12:60.
28. Puvitha RD, Shifa S. Breast Carcinoma, Receptor Status, and Her2 neu Overexpression Revisited. *Int J Sci Stud* 2016;3(10):52-8.
29. Tasneem S, Naseer F, Shahid S, Nasreen S, Khan MM, Javed N. A study of prognostic markers and stage of presentation of breast cancer in southern region of khyber pakhtunkhwa, Pakistan. *J. Med. Sci. (Peshawar, Print)* April 2012;20(2):63-6