Immunohistochemical Analysis of Breast Cancer at BP Koirala Memorial Cancer Hospital Nepal.

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Abstract

Introduction: Immunohistochemistry test is used to characterize intracellular proteins or various cell surfaces in all tissues. It is used to solve diagnostic problems or for determining prognosis and response to therapy in breast pathology. ER, PR and HER2 are well established biomarkers for breast cancer prognosis and for guiding treatment. **Materials and methods:** This is retrospective study at Department of Pathology of B P Koirala Memorial Cancer Hospital in Bharatpur, Chitwan, Nepal effective from 15 April 2020 to 14 April 2021. All the data were retrieved and analyzed. **Results:** Total 205 breast cancer cases were analyzed, among them 198 cases were females accounting 96.5 % and 7 cases were males accounting 3.5 %. Altogether 125 (60.9%) cases had immunohistochemistry panel of ER, PR and HER2 tests done. 48% cases were ER positive, 42.4% cases were PR positive, 34.4% were HER2 positive and 9.9% cases were triple negative. **Conclusion:** Breast cancer is more common in females than in males. Most common affected age group was 41-50 years. Most common histological type was invasive ductal carcinoma NST. In order to improve breast cancer outcomes and survival, early diagnosis, immunohistochemistry hormone analysis and screening tests should be done.

Keywords: Breast Cancer, Immmunohistochemistry, Nepal, Hormone status

Introduction:-

Breast cancer is a group of diseases in which cells in breast tissue change and divide uncontrolled, typically resulting in a lump or mass. Most breast cancers begin in the lobules (milk glands) or in the ducts that connect the lobules to the nipple. Breast cancer is the most common cancer and also the leading cause of cancer mortality in women worldwide. Approximately 1.38 million new breast cancer cases were diagnosed in 2008 with almost half of all breast cancer cases and nearly 60% of deaths occurring in lower income countries.

Globally, breast cancer impacting 2.1 million women each year, and also causes the greatest number of cancer-related deaths among women. In 2018, it is estimated that

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627,000 women died from breast cancer – that is approximately 15% of all cancer deaths among women. While breast cancer rates are increasing in nearly every region globally.

The breast cancer in females in the Western world, with a lifetime risk of the order of 1/10.[1] Similarly about 1 in 8 U.S. women (about 12%) will develop invasive breast cancer over the course of her lifetime.

High-income countries (HICs) have made the most progress in improving breast cancer outcomes attributable to the combination of improved earlier detection and effective adjuvant therapies. By contrast, breast cancer is an increasingly urgent problem in low and middle income countries (LMICs).[2]

Estrogen receptor and progesterone receptor (ER/PR) tests are used to help guide breast cancer treatment. Receptors are proteins that attach to certain substances. ER/PR tests look for receptors that attach to the hormones estrogen and progesterone in a sample of breast cancer tissue. Estrogen and progesterone play key roles in a woman's sexual development and reproductive functions. Men also have these hormones, but in much smaller amounts.

About 70 percent of all breast cancers in women have receptors that attach to estrogen and/or progesterone. About 80 percent to 90 percent of breast cancers in men have these receptors. Breast cancers with estrogen and/or progesterone receptors include the following types:

ER positive (ER+): Cancers that have estrogen receptors (ER)

PR positive (PR+): Cancers that have progesterone receptors (PR)

Hormone receptor positive (HR+): Cancers that have one or both types of these receptors.

Breast cancers without ER or PR receptors are known as hormone receptor HR negative (HR-).

ER/PR tests will show whether there are ER and/or PR receptors on breast cancer cells. Test results are frequently referred to as the hormone receptor status. Hormone receptor positive status will respond well to certain types of treatments like Tamoxifen therapy. The antitumor effects of tamoxifen are thought to be due to its antiestrogenic activity, mediated by competitive inhibition of estrogen binding to ER. As a consequence, tamoxifen inhibits the expression of estrogen-regulated genes, including growth factors and angiogenic factors secreted by the tumor that may stimulate growth by autocrine or paracrine mechanisms.

HER2 positive breast cancer is a breast cancer that tests positive for a protein called human epidermal growth factor receptor 2 (HER2). This protein promotes the growth of cancer cells.

In about 1 of every 5 breast cancers, the cancer cells have extra copies of the gene that makes the HER2 protein. HER2 positive breast cancers tend to be more aggressive than other types of breast cancer.

If the IHC result for HER2 is 2+, the HER2 status of the tumor is not clear and is called "equivocal." This means that the HER2 status needs to be tested with cytogenetic tests like FISH to clarify the result.

If the IHC result is 3+, the cancer is HER2 positive. These cancers are usually treated with drugs that target HER2. HER2 is an

established therapeutic target in a large subset of women with breast cancer; a variety of agents including trastuzumab, pertuzumab, lapatinib, neratinib and trastuzumab emtansine have been approved for the treatment of HER2-positive breast cancer.

Treatments that specifically target HER2 are very effective. These treatments are so effective that the prognosis for HER2 positive breast cancer is quite good.

Materials and methods

This is retrospective study at Department of Pathology in B P Koirala Memorial Cancer Hospital effective from 15 April 2020 to 14 April 2021. This study included the patients who were operated at BPKMCH or referred cases from elsewhere, but the specimen was processed and reported at BPKMCH. All the data were retrieved and analyzed.

Results

Total 205 breast cancer cases were analyzed, among them 198 cases were females accounting 96.5 % and 7 cases were males accounting 3.5 %.

Among 205 cases, 181 (88.6%) cases were invasive ductal Carcinoma No Special Type, 5 (2.4%) cases were malignant phylloides tumour, 4 (1.9%) cases were invasive lobular carcinoma, 4 (1.9%) cases were medullary carcinoma, 4 (1.9%) cases were squamous cell carcinoma, 3 (1.4%) cases were paget's disease of nipple with ductal carcinoma in situ, 2 (0.9%) cases were mucinous carcinoma, 1 (0.4%) case was invasive papillary carcinoma, 1 (0.4%) case was dermatofibrosarcoma protruberans.

Regarding grading of tumour, 111 (54%) cases were Grade II, 49 (24%) cases were Grade III, 45 (22%) cases were Grade I.

Among tumour size 119 (58.9%) cases were T2 size tumour, 36 (17.8%) cases were T3 size tumour, 25 (12.4%) cases were T4 size tumour, 22 (10.9%) cases were T1 size tumour.

Among nodal involvement by tumour cells 74 (36.6%) cases were N0 type, 63 (31.2%) cases were N1 type, 43 (21.3%) cases were N2 type, 22 (10.9%) cases were N3 type.

Table 1: Age-wise breast cancer distribution

Age group	Number of breast cancer cases	Percentage
Less than 20 Years	-	-
21-30 Years	9	4.4%
31-40 Years	46	22.4%
41-50 Years	66	32.2%
51-60 Years	52	25.4%
61-70 Years	21	10.2%
More than 70 Years	11	5.4%
Total	205	100%

Altogether 125 sample cases were processed and done immunohistochemistry ER, PR and HER2 tests. Among them 60 cases had ER positive accounting 48% cases whereas 65 cases had ER negative accounting 52% cases. Similarly 53 cases had PR positive accounting 42.4% cases and 72 cases had PR negative accounting 57.6% cases. Regarding HER2 test, 43 (34.4%) cases had HER2 positive and 70 (56%)cases had

HER2 negative whereas 12 (9.6%) cases were equivocal means 2+ respectively.

Similarly 18 (14.4%) cases were triple positive and 24 (19.2%) were triple negative.

Discussion

Breast cancer is a heterogeneous disease, comprising multiple entities associated with distinctive histological and biological features, clinical presentations and behaviors and responses to therapy.[3]

This study comprises 205 breast cancer patients of which 198 cases (96.5%) were females and 7 cases (3.5%) were males. Which is comparable to the study published by Pathak, R et al, in which females cases were 97.3% and male cases were 2.7%.[4]

According to the study carried by S Jamal et al, carcinoma of breast is one of the less frequent malignancies in males. In their study 50 cases of malignant tumors of male breast diagnosed during a 10 years period (1980-1989) were analyzed retrospectively. One male breast was involved for every 33 female cases. The peak incidence was between 5th to 7th decade with mean age of 58.54 years. Histologically, the infiltrating duct carcinoma (grade III) was the predominant lesion.[5] According to our study youngest male case was 23 years of age suffering from dermatofibrosarcoma protuberans others were 35 years, 53 years, 65 years, 66 years, 70 years and 72 years of age all suffering from invasive ductal carcinoma NST type.

According to our study, breast cancer was most common in the age group 41-50 years (32.2%). Our finding is very similar to Chavan, R et al, where they encountered maximum breast cancer in the age-group 40-50 years (38%).[6]

Shrestha JS et al did study, among 3270 total cancer patients, among them 5.59% (183patients) had breast cancer. Age range 40 to 49 was the most affected age group comparable to WHO data on the Nepal breast cancer status. The minimum age was 22 years and the maximum was 82 years. Left sided breast (51%) cancer was more common, followed by right sided (44%) and bilateral (4%). This result is comparable to the result of the similar study done in India where left sided cancer was more common than right sided.[7] In our study minimum age was 23 years and the maximum age was 92 years. Left sided breast cancer cases were 111 (54.15%) and right sided breast cancer cases were 94 (45.85%). So our study revealed that left sided breast cancer was more common than right sided breast cancer.

Breast cancers can be classified into biologically and clinically meaningful subgroups according to histological grade (Elston and Ellis, 1991) and histological type (Ellis et al., 1992). Grade is an assessment of the degree of differentiation (i.e. tubule formation and nuclear pleomorphism) and proliferative activity (i.e. mitotic index) of a tumour, and mirrors its aggressiveness (Elston and Ellis, 1991).

Histological type, on the other hand, refers to the growth pattern of the tumours. The histological diversity of adenocarcinomas in the breast has long fascinated pathologists, who have identified specific morphological and cytological patterns that were consistently associated with distinctive clinical presentations and/or outcomes. These patterns are called ‘histological

types'. The commonest type of breast carcinoma is the so-called invasive ductal carcinomas not otherwise specified (IDC-NOS) or of no special type (IDC-NST).[8]

In our study we did grading based on Nottingham grading system. According to our study 111 (54%) cases were Grade II cancer, 49 (24%) cases were Grade III cancer and 45 (22%) cases were Grade I cancer. Which is comparable to the study carried by Chavan, R., & Prasad, A, in which they found out of 150 patients, 55% cases were diagnosed with Nottingham grading system grade II of breast cancer.[6]

According to our study most common histological type was invasive ductal carcinoma NST 181 (88.6%) cases, followed by malignant phylloides tumour 5 (2.4%) cases, invasive lobular carcinoma 4 (1.9%) cases, medullary carcinoma 4 (1.9%) cases, squamous cell carcinoma 4 (1.9%) cases, Paget's disease of nipple with ductal carcinoma in situ 3 (1.4%) cases, mucinous carcinoma 2 (0.9%) cases, invasive papillary carcinoma 1 (0.5%) case, dermatofibrosarcoma protuberans 1 (0.5%) case respectively. Similarly, 58.9% cases were at T2 stage, 17.8% cases were at T3 stage, 12.4% cases were at T4 stage and 10.9% cases were at T1 stage. 36.6% cases were at N0 stage, 31.2% cases were at N1 stage, 21.3% cases were at N2 stage and 10.9% cases were at N3 stage. These findings suggest that most of the cases were in advanced stage.

According to the Grethe Albrektsen et al ductal tumors, the most common histological type, accounted for 81.4% of all cases, followed by lobular tumors (6.3%) and unspecified carcinomas (5.5%).[9] Stage II (49.1 %) was the most common stage at diagnosis. 83% patients had a tumor size of 2-5 cm with average size of 3.25 cm at presentation. Majority of patients presented with Stage IIa and IIIa disease breast cancer.[7]

Pathak, R et al did study comprising 112 breast cancer patients of which invasive ductal carcinoma no specific type was the most common type of breast carcinoma, 84 cases accounting 75% of total cases. Carcinoma with medullary features was second most common (6 cases) comprising 5.4% cases followed by lobular, papillary, apocrine, mucinious and NST mixed types. Grade II tumors were most frequent grade observed in 76.79% cases followed by Grade I (12.50%) and Grade III (10.71%). The tumors were found at T2 and N3 stage i.e maximum at grade II.[4]

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are well established biomarkers for breast cancer prognosis and for guiding treatment. Altogether 125 cases had done immunohistochemistry ER, PR and HER2 tests. Among them 60 cases had ER positive accounting 48% cases whereas 65 cases had ER negative accounting 52% cases. Similarly 53 cases had PR positive accounting 42.4% cases and 72 cases had PR negative accounting 57.6% cases. Regarding HER2 test, 43 (34.4%) cases had HER2 positive and 70 (56%) cases had HER2 negative whereas 12 (9.6%) cases were equivocal means 2+ respectively.

Similarly 9 (9.9%) cases were triple positive and 24 (25.6%) were triple negative.

In our study 60 cases were ER positive accounting 48% which is similar with the study done by Shukla A et al. Shukla A et al.

did single institutional study of 112 cases of breast cancer patients from North India suggest that mean age of breast cancer patient is 53.70±12.47 with ER positivity of 49.1%, not grossly different from rest of the country but significantly lower than western.[12]

According to the Rekha Vijay Kumar et al a total of 5436 patients were included with a median age of 48 years. Among these, 65% were ≤ 55 years. The overall incidence of hormone receptor (HR) positive patients was 48%; HER2 positive 15%; and triple-negative breast cancer (TNBC) 37%.[13]

According to the Urmila Devi P et al. HER2/neu negative expression was seen in 51.61% of cases. Triple negative receptor expression was seen in 54.83% of infiltrating ductal carcinoma.[14]

Breast cancer has emerged as the second more prevalent malignancy in women in Nepal. But the hospital records show that Nepali women reach to get medical help when the disease is already in an advanced stage.[10]

Factors responsible for the general delayed diagnosis are lack of knowledge, limited breast cancer screening programs, limited health care facilities and sociocultural barriers. The government should foster novel policies to establish effective nationwide cancer literacy programmes, as well as engagements with community-level, national and international organizations and the healthcare system.[11]

In order to improve breast cancer outcomes and survival, early detection is critical. There are two early detection strategies for breast cancer: early diagnosis and screening. Limited resource settings with weak health systems where the majority of women are diagnosed in late stages should prioritize early diagnosis programmes based on awareness of early signs and symptoms and prompt referral to diagnosis and treatment.

Conclusion

Breast cancer is more common in females than in males. Most common affected age group was 41-50 years. Majority of cases were diagnosed with Nottingham grading system grade II of breast cancer. Most common histological type was invasive ductal carcinoma NST and mostly cases were in advanced stage. The molecular classification of breast cancer is based on the immunohistochemistry analysis of breast cancers. Researchers use molecular subtype of breast cancers when developing treatment standards of care and when developing new treatments.

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