

Study of estrogen receptor, progesterone receptor, and HER-2/neu status in breast carcinoma



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ABSTRACT

Background: Breast cancer treatment depends mainly on hormone receptors (estrogen and PRs) and human epidermal growth factor receptor-2 (HER2)/neu profile. These receptor analyzes determine the patient's prognosis, treatment, and outcome. **Aims and Objectives:** The main objective of this study was to correlate the histologic grade of breast carcinoma with hormone receptors and HER2/neu status. **Materials and Methods:** This is a retrospective analysis of 342 patients treated from January 2016 to December 2021 at Manipal Teaching Hospital, Pokhara, Nepal to determine hormone receptors and HER2/neu status in breast carcinoma. Modified radical mastectomy, breast-conserving surgery, toilet mastectomy, and excisional biopsies were included for statistical correlation between hormone receptors, HER2/neu, histologic grade, and lymph node status. **Results:** The mean age of the patients was 48.43 ± 9.4 years (29–71). Of the 342 patients, 334 (97.7%) were female and 8 (2.3%) were male. Left breast carcinoma was 5.3% more common than right breast carcinoma. Among them, 34 (9.9%), 245 (71.6%), and 63 (18.4%) were grade I, II, and III, respectively. Grade II were the most common cancer. The smallest tumor size was 0.5 cm and the largest tumor size was 14 cm. Lymph node involvement was 226 (66.1%). The most common histology was invasive ductal carcinoma with 282 (82.5%), lobular carcinoma with 47 (13.8%), medullary carcinoma with 9 (2.6%), and mucinous carcinoma with 4 (1.2%). Immunohistochemical analysis of all breast cancer patients in the present study revealed ER 175 (51.2.7%), PR 146 (42.7%), and HER2/neu 93 (27.2%). Of all male patients, ER was 100% positive, PR was 75% positive, and HER2/neu was 25% positive. According to grading, ER was seen positive in 23 (13.1%) in grade I, 112 (64%) in grade II, and 40 (22.8.1%) in grade III carcinoma ($P < 0.05$). Similarly, PR was 19 (13.1%) in grade I, 95(65.9%) in grade II, and 30 (20.8%) in grade III carcinomas ($P < 0.05$). Moreover, Her/2-neu was 7 (7.5%) in grade I, 63 (67.3%) in grade II, and 23 (24.7%) in grade III carcinomas ($P < 0.05$). In HER2/neu positive cases, it was observed that the positive expression of estrogen receptor (ER) was high as compared to PR. **Conclusion:** ERs, PRs, and HER2/neu are the most important factors that determine the best treatment, prognosis, and outcome in breast carcinoma.

Key words: Breast carcinoma; Estrogen receptor; Progesterone receptor

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women. Nearly 1 million cases are diagnosed each year and there were approximately 375,000 deaths worldwide in 2000.¹ The leading cause of death in women aged 45–55 years is breast cancer.² Based on the hormone receptor,

the disease is classified into different subtypes.³ The most important prognostic factors in breast carcinoma depend on tumor size, lymph node involvement, histologic subtype, and histologic grade.^{4,5} In some cases, prognosis may differ despite the same tumor size and stage.⁶ Different types of biomarkers are used to determine the prognosis and find the best adjuvant treatment for

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patients. These biomarkers help to distinguish between low and high risk disease. This can save unnecessary and costly adjuvant treatment and identify high-risk patients to start appropriate aggressive treatment immediately.^{6,7} Determination of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2/neu) receptor status in breast cancer is becoming increasingly important in medical practice nowadays for better management. In many clinical trials, positive hormone receptor status has been shown to provide a survival benefit when treated with adjuvant hormonal or chemotherapeutic therapies.⁸ In the treatment of breast carcinoma, ER and PR play a critical role in the growth and progression of breast carcinoma.⁵ It is already proven that strongly ER-positive cases benefit from endocrine therapy alone than those with low to moderate ER-positivity.⁹ The PR-status alone is associated with overall survival and disease-free survival. Patients with ER and PR positive tumors have a better outcome than those with negative ER and PR expression.¹⁰ HER2/neu encodes a transmembrane glycoprotein with tyrosine kinase activity known as p185, which is related to epidermal growth factor. Many studies have shown that overexpression of HER2/neu results in poor response to tamoxifen and decreased overall survival.¹¹⁻¹³ Routine analyzes of these immunohistochemical receptors are performed for predictive purposes in the treatment of breast cancer patients. Successful strategies and protocols for the early detection and screening of the disease need to be maintained to reduce mortality.

Aims and objectives

The main objective of this study was to correlate the histologic grade of breast carcinoma with hormone receptors and HER2/neu status.

MATERIALS AND METHODS

This retrospective study was conducted on 342 kerosene blocks from patients who underwent modified radical mastectomy, breast-conserving surgery, and toilet mastectomy at Manipal Teaching Hospital from January 2016 to December 2021. All samples were collected after ethical clearance and informed consent. Proper histological pathology report of the patients was done which included age, size, grade, and lymph node status. The tumor size of the patients was divided into Group I (<2 cm), Group II (2–4.9 cm), and Group III (>5 cm). Bloom-Richardson scoring was used for histological grading (grade I, II, and III) and all parameters were reviewed by the pathologist. The lymph node status of the patient was collected in two groups (<4 cm and >4 cm). Quantitative values of the data were expressed as mean±SD.

SPSS software version 11.0 was used for statistical analysis. Chi-square test and t-test were applied to determine the association between ER, PR, and HER2/neu expression with various clinicopathological factors such as age, tumor size, grade, and lymph node status.

RESULTS

From January 2016 to December 2021, there were 342 cases of breast carcinoma patients. The minimum age of patients was 29 years and the maximum age was 71 years. The average age of patients was 48.43±9.4 years. Of the 342 patients, 334 (97.7%) were female and (2.3%) were male. Left breast carcinoma was more common than right breast carcinoma, 52.6% on the left, and 47.3% on the right. Histology Grades I, II, and III were 34 (9.9%), 245 (71.6%), and 63 (18.4%), respectively. Grade II was the most common cancer. The smallest tumor was 0.5 cm and the largest was 14 cm. Lymph nodes were positive in 226 (66.1%). Among these lymph node positive cases, 105 (30.7%) were larger than 4 cm and 121 (35.4%) were smaller than 4 cm. The most common histology was invasive ductal carcinoma 282 (82.5%), followed by lobular 47 (13.8%), medullary 9 (2.6%), and mucinous 4 (1.2%) carcinomas.

Immunohistochemical analysis of the total breast cancer patients in the present study revealed 175 (51.2%) ERs, 146 (42.7%) PRs, and 93 (27.2%) HER2/neu. In the eight male patients, ER was 100% positive, PR 75% positive, and HER2/neu 25% positive. According to histological grading, 23 (13.1%) ER positive cases were in grade I, 112 (64%) in grade II, and 40 (22.8%) in grade III carcinoma ($P<0.05$). Similarly, PR was 19 (13.1%) in grade I, 63 (67.3%) in grade II, and 23 (24.7%) in grade III carcinomas ($P<0.05$). Similarly, HER-2/neu was 7 (7.5%) in grade I, 63 (67.7%) in grade II, and 23 (24.7%) in grade III carcinomas ($P<0.05$). According to lymph node size, in <4 cm lymph nodes 52 (36.7%) were ER, 57 (52.7%) were PR, and 41 (59.4%) were HER2/neu positive. At >4 cm, 52 (44.8%) were ER positive, 51 (47.2%) were PR positive, and 28 (40.6%) were HER2/neu positive. According to tumor size, cases were divided into Group I (<2 cm), Group II (2–4.9 cm), and Group III (>5 cm). Among them, 32 (9.4%) were in Group I, 173 (50.6%) were in Group II, and 135 (39.5%) were in Group III. The correlation between tumor size and receptors in Group I ER was 22 (12.6%), PR 14 (9.5%), and HER2/neu 12 (12.9%), in Group II, ER 85 (48.8%), PR 69 (47.2%), and HER2/neu 47 (50.5%), and in the Group III ER 67 (37.7%), PR 63 (43.1%), and HER2/neu 34 (36.5%) (Table 1).

Table 1 : Correlation of ER, PR, and HER-2/neu status with grade, tumor size, and lymph node metastases

	ER+ n=175	PR+ n=146	HER2/neu+ n=93
Grade I	23 (13.1%)	19 (13.1%)	7 (7.5%)
Grade II	112 (64%)	95 (65.95%)	63 (67.3%)
Grade III	40 (22.8%)	30 (20.8%)	23 (24.7%)
P<0.05			
<2 cm	22 (12.6%)	14 (9.5%)	12 (12.9%)
2–4.9 cm	85 (48.8%)	69 (47.2%)	47 (50.5%)
>5 cm	67 (37.7%)	63 (43.1%)	34 (36.5%)
P-value			
No L/N			
<4 cm L/N	52 (36.7%)	57 (52.7%)	41 (59.4%)
>4 cm L/N	52 (44.8%)	51 (47.2%)	28 (40.6%)
P<0.05			

ER: Estrogen receptor, PR: Progesterone, HER2/neu: Human epidermal growth factor receptor2

DISCUSSION

The present study was conducted on 342 patients with breast cancer of different histology in a single institution of Manipal Teaching Hospital, Pokhara, Nepal. Integration of clinical pathology and cancer biology is required for the best treatment approach and prognosis of breast cancer patients. The hormone receptors ER, PR, and HER2/neu are routinely investigated for adjuvant hormonal and targeted therapy in the treatment of breast cancer.^{14,15} The mean age of patients in our study was 48.43±9.4 years, which is almost comparable to other studies in Nepal.^{16,17} Patients diagnosed at <35 years of age had a very poor prognosis compared to older patients. The study conducted by Kataoka et al., had shown that younger patients <35 years of age had a poor prognosis compared to older patients.

Our results of ER, PR, and HER2/neu have shown significant association with various clinicopathological factors. In the present study conducted in our institution, the rate of ER/PR positivity (51.2%/42.7%) was almost identical to the results done in Nepal and other parts of the world.¹⁸⁻²⁰ In most of the studies done in the different hospitals of Nepal, the ER/PR positivity status was between 20% and 50%.^{16,17,20,21} Compared to other parts of developed western countries, the outcome of our receptor was not similar. Kapić et al., showed in his study that the number of receptor positive cases in western developed countries is high up to 60–80%.²² The difference between them and us could be due to races, average age at diagnosis, and possibly genetic signature. In the present study, ER negativity and positivity were almost equal overall, while, in PR, the negative expression was greater. The proportion of HER2/neu-positive cases was 27.2%, which is consistent with the study by Slamon and Clark et al.²⁴ In the HER2/neu-positive cases, it was observed that the positive

expression of ER was higher compared to PR. The same study conducted by Biesterfeld and Schroder and Slamon and Clark was not comparable to our study, which could be due to race, average age at diagnosis, body mass index, or genetic signature.^{23,24} In addition, variation in receptor positivity has been reported in the Asian population.^{25,26} A study conducted in different oncology centers showed positive expression of the receptors ER, PR, and HER2/neu in elderly patients, which is comparable to our study.²⁷ Negative expression of ER and HER2/neu was also higher in young patients.²⁸ In our study, we found that grade II tumors were more common, followed by grade III and I tumors, which is consistent with the study by Kaul et al.²⁹ However, our study is in contrast to some other studies, in which well-differentiated breast cancer is more common than poorly differentiated cancer.^{28,30}

The correlation of ER and PR with grade I and II was very similar to other studies.³¹ However, there was no significant correlation between the expression of HER2/neu and with a positivity of 7.5% in grade I, 67.7% in grade II, and 24.7% in grade III (p-value > 05). Other studies performed by Dayal et al., Geethamala et al., and Emmanuel et al.,⁷ have also shown similar results.^{18,19,32} HER2/neu is an epidermal growth factor located on the surface of a cell that transmits growth signals to the nucleus. Overexpression of the HER2/neu receptor is associated with a poor prognosis. Overexpression of HER2/neu is an independent prognostic factor. In our study, no significant association was found between the expression of ER, PR, HER2/neu, and lymph node metastasis. Similar results have been reported in many other studies.^{1,33} In contrast to our results, Tokatli et al., Fatima et al., and Richard had found a significant association between HER2/neu expression and increased positive lymph node metastasis status.³⁴⁻³⁶ Our results compared with other studies <4 positive lymph nodes were more likely to show no receptor reactivity (ER, PR, and Her2/neu) than >4 positive lymph nodes, which is in contrast to other studies.^{25,28} The majority of specimens in our study were infiltrating ductal carcinomas, and only a few were lobular type. However, in our study as well as other studies, no significant association was found between the expression of ER, PR, HER2/neu, and histological type.²²

Limitations of the study

The Study has its limitation. We investigated the biomarkers only those patients who were treated only in Manipal Teaching Hospital.

CONCLUSION

The study we conducted is almost similar to the Indian subcontinent. However, our studies differ from those of

western or developed countries due to age at diagnosis, body mass index of races, gene signature, or other reasons, in which they revealed higher number of ER/PR-positive cancers. These prescriber tests are somewhat more expensive than in other countries, but they are essential for the best treatment, prognosis, and outcome for the patient.

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RKS – Concept and design, review of literature, statistical analysis, and interpretation, manuscript preparation and revision; **AL** – Data collection, literature search and review; **PG** – Manuscript revision and literature review and statistical analysis.

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