

CLINICAL STUDY OF OESTROGEN RECEPTOR, PROGESTERONE RECEPTOR AND HER 2/ NEU RECEPTOR EXPRESSION STATUS IN BREAST CANCER PATIENTS

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ABSTRACT

Hospital-based descriptive study was done from January 2017 to December 2017. The study was carried out in 100 breast cancer patients, attending the Medical Oncology Department of Yangon General Hospital by using convenience non-probability sampling method. The positive expression rate of ER, PR receptors observed were 53% and 57 % respectively. Her2/neu positive expression was 34% and equivocal (8%). The mean age of breast cancer patients was 51.1 years with the youngest being 26 and the oldest,78. Statistically significant association was found in positive/negative expressions of ER and different age groups. The positive expression of ER found was higher in > 40 years aged groups whereas negative expression of ER found was higher in <40 years aged group (p=0.04). The positive expression of PR was also found higher in > 40 years aged groups whereas negative expression of PR found was higher in <40 years aged group but it was not significant statistically (p=0.09). A statistically significant association was observed between tumor grade and ER, PR receptor expression. Positivity of ER, PR was found mostly in grade I tumor, (both are 90%) and negativity of ER, PR was found mostly in grade III tumor, (both are 62.1%). Expression of ER and PR was found to be significantly associated with tumor grade (p=0.02 and p=0.01 respectively). Patients with larger tumor size have trend towards association with

negative hormone receptor expression. Her2/neu receptor expression did not reveal significant association with clinical parameters. Triple negative breast cancer patients were associated with younger age, higher tumor grade, larger tumor size and lymph node positivity in this study.

Key Words; oestrogen receptor, progesterone receptor, her2/neu receptor, breast cancer

INTRODUCTION

Breast cancer is the most common malignant tumor and a leading cause of cancer deaths in women worldwide. In Myanmar, breast cancer is most common cancer in female and second most common cancer in all patients according to cancer registry YGH 2014. According to the cancer registry of Yangon General Hospital, there were 738 cases of breast cancer in the year 2006. In 2012 the breast cancer cases were 1330 and in the year 2014 there were 1362 female cases and 2 male cases showing a rising trend.

Internationally, the goal of treatment in breast cancer is cure from stage I to III diseases. Several well-established prognostic and predictive factors are universally used to guide the clinical management of women in breast cancer. Testing of hormone receptor and Her2/neu receptor status is essential in managing breast cancer. As these guide the treatment option, serve as prognostic markers, they must be done in every case of breast cancer. In Myanmar, in the past, they

could not be done in most of the patients due to financial constraint as well as lack of availability. In fact, we would like to do these tests in breast cancer patients as much as possible. Therefore we conducted this study in main cancer center of Myanmar.

MATERIALS AND METHODS

Hospital-based descriptive study was carried out on 100 breast cancer patients admitted to Medical Oncology Department of Yangon General Hospital during January 2017 to December 2017. Pathological investigation (histology for locoregional staging and IHC for ER, PR, HER 2/neu receptor) was done. The status of ER, PR, HER 2 receptor in different age, histological staging, histological types and grading of tumor were analyzed..

RESULTS

During study period of one year, we studied 100 breast cancer patients. ER positive rate was 53% and negative rate is 47%. PR positive rate was 57% and negative rate is 43%. Her2/neu receptor was positive in 34%, equivocal in 8% and negative in 58%. Patients with equivocal Her2 receptor cannot precede FISH due to resource limitation.

Breast carcinoma patients were categorized in different age groups. 12% in <40 year age group, 38% in 40-49 year age group, 31% in 50-59 year age group and 19% in 60 year and above age group. The mean age was 51.1 years. In <40 year age group, ER was positive in 16.7% and PR was positive in 33.3%. In 40-49 year age group, ER was positive in 63.2% and PR was positive in 71.1%. In 50-59 year age group, both ER and PR were positive in 51.6%. In ≥ 60 year aged group, ER was

positive in 57.9% and PR was positive in 52.6%. In <40 year age group, HER2 receptor was positive in 41.7%, negative in 50% and equivocal in 8.3%. In 40-49 year age group, HER2 receptor was positive in 28.9% negative in 65.8% and equivocal in 5.3%. In 50-59 year age group, HER2 receptor was positive in 38.7%, negative in 51.6% and equivocal in 9.7%. In ≥ 60 year age group, HER2 receptor was positive in 31.6%, negative in 57.9% and equivocal in 10.5%

Among 100 breast cancer patients, most cases were of B&R tumor grade II (61%) followed by grade III (29%) and grade I (10%). In B&R tumor grade I tumors, both ER and PR were positive in 90%. In B&R tumor grade II tumors, ER was positive in 54.1% and PR was positive in 60.7%. In B&R tumor grade III tumors, both ER and PR were positive in 37.9%. In B&R tumor grade I tumors, HER2 receptor was positive in 10%, negative in 80% and equivocal in 10%. In B&R tumor grade II tumors, HER2 receptor was positive in 37.7%, negative in 52.5% and equivocal in 9.8%. In B&R tumor grade III tumors, HER2 receptor was positive in 34.5%, negative in 62.1% and equivocal in 3.4%.

Among 100 breast cancer patients, histological stage I was 3%, stage IIA was 25%, stage IIB was 19%, stage IIIA was 19%, stage IIIB was 23%, stage IIIC was 4% and stage IV was 7%. Among 100 breast cancer patients, tumor sizes <2cm (T1) were 5%, 2-4.9cm (T2) were 49% and ≥ 5 cm (T3) were 46%. Lymph node positive cases were 62% and negative cases were 38%. In stage I tumors, ER was positive in 33.3%. In stage IIA tumors, ER was positive in 56%. In stage IIB tumors, ER was positive in 37.9%. In stage IIIA tumors, ER was positive in 52.6%. In

stage IIIB tumors, ER was positive in 47.8%. In stage IIIC tumors, ER was positive in 25%. In stage IV tumors, ER was positive in 57.1%. In stage I tumors, PR was positive in 33.3%. In stage IIA tumors, PR was positive in 64%. In stage IIB tumors, PR was positive in 63.2%. In stage IIIA tumors, PR was positive in 57.9%. In stage IIIB tumors, PR was positive in 52.2%. In stage IIIC tumors, PR was positive in 50%. In stage IV tumors, PR was positive in 42.9%. In stage I tumors, HER2 was positive in 66.7% and equivocal in 0%. In stage IIA tumors, HER2 was positive in 32% and equivocal in 0%. In stage IIB tumors, HER2 was positive in 42.1% and equivocal in 10.5%. In stage IIIA tumors, HER2 was positive in 26.3% and equivocal in 21.1%. In stage IIIB tumors, HER2 was positive in 17.4% and equivocal in 4.3%. In stage IIIC tumors, HER2 was positive in 100%. In stage IV tumors, HER2 was positive in 42.9% and equivocal in 14.3%.

In tumor sizes <2cm (T1), both ER and PR were positive in 60%. In tumor sizes 2-4.9cm (T2), ER was positive in 59.2%, PR was positive in 67.3%. In tumor sizes \geq 5cm (T3), ER was positive in 46%, PR was positive in 45.7%. In tumor sizes <2cm (T1), HER2 was positive in 40% and equivocal in 0%. In tumor sizes 2-4.9cm (T2), HER2 was positive in 32.7% and equivocal in 6.1%. In tumor sizes \geq 5cm (T3), HER2 was positive in 34.8% and equivocal in 10.9%.

Among lymph nodes positive patients, ER was positive in 56.5% and PR was positive in 59.7%. Among lymph nodes negative patients, ER was positive in 47.4% and PR was positive in 52.6%. Among lymph nodes positive patients, HER2 was positive in 32.3% and equivocal in 9.7%.

Among lymph nodes negative patients, HER2 was positive in 36.8% and equivocal in 5.3%.

Three Histological types; invasive ductal carcinoma (IDC) non special type (NST), invasive ductal carcinoma (special type) and invasive lobular carcinoma (ILC) was found in the present study; IDC (NST) type (92%), IDC (special type) (4%) and ILC type (4%). IDC (NST) expressed ER in 53.3% and PR in 57.6%. IDC (special type) expressed ER in 25% and PR in 25%. Lobular carcinoma type expressed ER in 75% and PR in 75%. In IDC (NST), HER2 was positive in 57.6% and equivocal in 7.6%. In IDC (special type) HER2 was positive in 25% and equivocal in 25%. In Lobular carcinoma type HER2 was positive in 0%, negative in 100% and equivocal in 0%.

Among 18 triple negative breast cancer patients, < 40 year were 16.6%, 40-49 year were 39%, 50-59 year were 27.8% and \geq 60 year were 16.6%. Tumor grade II were (50%) and grade III were (50%). There was no tumor grade I in triple negative patients. IDC was 89%. ILC was 5.5% and special type including cribriform, papillary, mucinous and medullary type was 5.5%. In 72% of patients, tumor sizes are more than or equal to 5cm. 5.8% of patients was found to have tumor sizes <2cm and 22.2% of patients are 2-4.9 cm. Lymph node positive cases were 66.7% and negative cases were 33.3%.

Among 100 breast cancer patients, Her2/neu receptor was positive in 34%, equivocal in 8% and negative in 58%. Patients with equivocal Her2 receptor cannot proceed to FISH due to resource limitation.

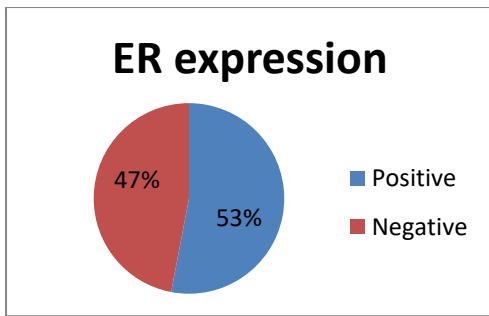


Figure1. Distribution of ER status of tumor among the patients (n=100)

Among 100 breast cancer patients, ER positive rate was 53% and ER negative rate is 47%.

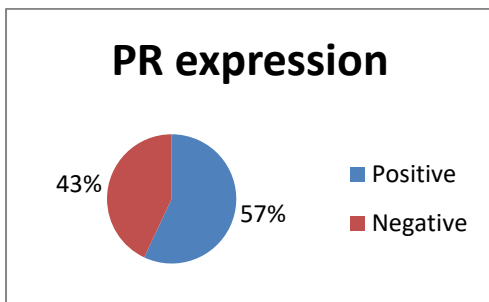


Figure2. Distribution of PR status of tumor among patients (n=100)

Among 100 breast cancer patients, PR positive rate was 57% and negative rate is 43%.

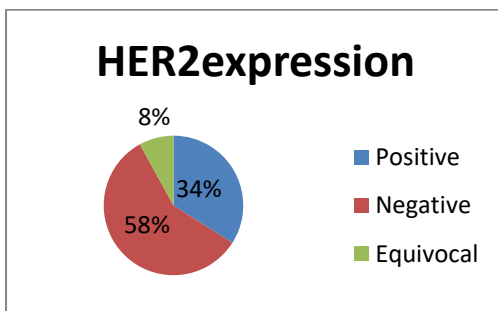


Figure3. Distribution of Her2 receptor status of tumor among patients (n=100)

DISCUSSION

Over the 12-month period (January 2017 to December 2017), there were 589 cases of breast cancer patients at the Medical Oncology Department of Yangon General Hospital. Out of 589 cases, 100 cases were tested for ER, PR, HER2/neu receptors were studied.

In the present study, positive expression of ER and PR was found to be 53% and 57% respectively. The negative expression of ER, PR receptors was 47%, 43% respectively and found lower than the positive expression. It correlates well with data of South East Asia region (Bhoo-Pathy et al, 2012)¹. In this regional study, positive expression of ER, PR and Her2/neu was found to be 56.6% and 52.4% respectively and this is in line with the result of the present study. However, overall positivity rate for ER and PR was lower than that reported in Western literature. In European and American population, 60–80% patients were found to be with positive receptor expression. This may be due to lower average age at diagnosis or racial difference.

It is established that the hormonal status differs amongst different ethnic groups. It was reported that ER and PR expression were lower in Asian Filipino breast cancer patients compared to Asian American breast cancer patients. In addition, ER status of Malay, Chinese and Indian women with breast cancer living in Singapore and Malaysia was reportedly different amongst these three ethnic groups. The variation of hormonal status among breast cancer patients with different races may be attributed to genetic disparities and socioeconomic factors such as life style, nutritional status and environmental exposure.

Another finding of the study was that Her2/neu positive expression was 34%, negative expression was 58 % and equivocal in 8%. In the study by Al-Khayat et al, 2016, positive expression of Her2/neu was found to be 29.8%. Therefore, there was only a minimal difference with the findings of this study. In contrast, the result differed with that of regional study (Dr. Myat Soe Khaing, 2008)². In this regional study, 22 breast cancer patients were included and 18.2% (4 out of 22) were found Her2/neu receptor positive.

Breast carcinoma patients were categorized into different age groups from less than 40 years to greater than 60 years. The mean age was 51.1 years with the youngest being 26 and the oldest; 78. Statistically significant association was found in positive/negative expressions of ER and different age groups. The positive expression of ER was found higher in > 40 years aged group whereas negative expression of ER was found to be higher in <40 year age group ($p=0.04$). The positive expression of PR also found was also higher in > 40 year age group whereas negative expression of PR was found to be higher in <40 year age group but it was not statistically significant ($p=0.09$). Therefore, younger patients were associated with negative hormone receptor expression than older patients (DeVita et al, 2011)³. According to DeVita et al, 2011, younger patients have low hormone receptor expression. No statistically significant association was found in positive/negative expressions of HER2 and different age groups.

More cases were of grade II (61%) followed by grade III (29%) and grade I (10%). This means that most tumors are

diagnosed when they progress to the histological grade of II. Thus it is necessary to educate the women about breast cancer, the importance of regular breast self-examination and urgent consultation of physician in case of development of any symptom. This will help in early diagnosis of breast cancer. Positivity of ER, PR was found mostly in grade I tumor, (both are 90%) and negativity of ER, PR was found mostly in grade III tumor, (both are 62.1%). Expression of ER and PR was found to be significantly associated with tumor grade ($p=0.02$ and $p=0.01$) respectively.

Most cases were of grade II (54.4%) followed by grade III (30.7%) and grade I (14.9%). The journal also showed that hormone receptors (ER and PR) were correlated significantly with grade of the tumor (Al-Khayat et al, 2016)⁴, so, finding from current study is similar to above study. However, this is in contrast to some studies where well-differentiated breast cancer is more common than the poorly differentiated cancer. In this study, ER and PR correlated well with tumor grade but Her2/neu expression did not reveal a significant association with tumor grade. Similar results were reported by other studies. Dr. Myat Soe Khaing (2008) also did not find statistically significant correlation between tumor grading and Her2/neu status. But, Al-Khayat et al, 2016 showed significant correlation between tumor grading and Her2/neu status.

Regarding tumor size, association of ER expression with tumor size was found. ER expression was found in 60% of tumor size <2cm but only 45.7% were tumor size >5cm but it was not statistically significant ($p=0.42$). PR expression was found in

tumor size of 2-5cm (67.3%) and followed by tumor size <2cm (60%) and noted in only tumor size >5cm (45.7%) (p=0.08). This is similar with Yadav et al, 2016 which showed significant association of tumor size with ER and PR expression (Yadav et al, 2016)⁵. In contrast to our results, Al-Khayat et al, 2016 did not show significant association of tumor size with ER and PR expression. There is no association between ER, PR expression and lymph node status (p=0.37 and 0.49) respectively. ER, PR expression did not also show significant association with clinical staging.

The difference in distribution of HER2 in different clinical stage was significant (p=0.02) and not significant regarding tumor size and lymph node. In the study by Al-Khayat et al (2016), no statistically significant association of Her2/neu expression with both tumor size and lymph node was demonstrated. Similar results have been documented in many other studies. Some similar studies found that majority of lymph node positive patients found to have Her2/neu positive expression. Due to resource limitation, patients with equivocal Her2 expression could not proceed to FISH test. Therefore, it was impossible to conclude the association of Her2/neu expression with clinical parameters well.

Three histological types were found in the present study. They were invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and special types of invasive ductal carcinoma including cribriform, papillary, mucinous and medullary type. The majority was invasive ductal carcinoma type, and only a few were lobular type and special type. IDC type was 92 %, IDC (special type) was 4%

and ILC type was 4%. However, the present study, as well as others, did not find a significant association among expression of ER, PR, Her2/neu and histological types. Yadav et al, 2016 also did not show association of receptor expressions with histological types.

There were total 18 in number of triple negative breast cancer patients. Triple negative patients were most common among 40-49 age group. Theoretically, triple negative breast cancers occur in younger patients and therefore this study correlate with theory background. These patients have tumor grade II (50%) and grade III (50%). There is no tumor grade I in these patients. Triple negative breast cancer associated with high B&R tumor grade showing grade III for 76.3% (Onitilo et al, 2009)⁶. Therefore, there was only a slight difference with the findings of this study.

In 72% of patients, tumor sizes are more than or equal to 5cm and are commonest. 5.8% of patients have tumor sizes <2cm and 22.2% of patients have 2-4.9 cm. So, triple negative patients presented with larger tumor size. Majority of patients are lymph nodes positive (66.7%) and others are lymph node negative. These correlated with DeVita et al (2011). The most common histological type is IDC and 89%. Other types, both ILC and special type, are the least common with 5.5% only.

A statistically significant association was observed between progressing tumor grade and ER, PR receptor expression with a p value of 0.02 and 0.01 respectively. Regarding different age groups, the differences in the distribution of ER in age groups were statistically significant while the differences regarding PR in different

age groups were towards the significant trend. In this study, no statistically significant association was observed between tumor sizes, with receptor expression. However, from the differences in percentages, a definite trend was evident. Patients with larger tumor size had increased association with unfavorable receptor expression than for patients with smaller tumor size. There was no significant association between expression of ER, PR with lymph nodes and histological types. Her2/neu receptor expression showed association with clinical stage but did not reveal association with other factors.

Despite the limitation due to the small sample size, tumor histological grade, patient age, tumor size and lymph node stage can be identified as important predictive and prognostic factors for breast cancer.

CONCLUSION

Breast cancer is the most common malignancy in Myanmar women according to data of Medical Oncology Department of Yangon General Hospital. Breast cancer has long-term disease free survival with the institution of timely and appropriate therapy. Improved breast cancer treatment requires integration of clinical pathology and cancer biology which could affect patient outcome. ER, PR and her2/neu are well-established procedures in routine breast cancer management for both prognostic factors and predictive factors. It can predict the response to adjuvant hormone therapy and anti Her2 therapy. This study revealed the significant association of different clinicopathological factors with an expression of ER, PR and Her2/neu receptor.

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