

Analysis of Prognostic Factors in Early Stage and Locally Advanced Breast Cancer

Alkesh Gamit¹, Varsha Galani^{2*} and Nikunj Vithlani³

¹A R College of Pharmacy & G H Patel Institute of Pharmacy, India

²Indukaka Ipcowala College of Pharmacy & G. H. Patel Institute of Pharmacy, India

³Bharat Cancer Hospital and Research Institute, Nirali Memorial Radiation Centre, India

***Corresponding author:** Dr. Varsha J Galani, Department of Pharmacology, Indukaka Ipcowala College of Pharmacy, New Vallabh Vidhyanagar 388121, Gujarat, India, Tel no: (+91)9429161203; Email: vrp173@yahoo.com

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Abstract

Breast cancer is the most common malignancy in women, and it is highly curable if diagnosed at an early stage. Present study was designed to identify prognostic factors for early stage and locally advanced breast cancer patients in Gujarat. This retrospective study (n=100) was conducted on patients visiting Bharat Cancer Hospital and Research Institute, Saroli, Surat, Gujarat. Data were collected by the case report forms and analyzed for the age, menstrual status, risk factors, axillary nodal status, tumor size and type, therapy, and hormonal receptor status. Response and survival rate due to the therapy were also analyzed according to the different age groups. The breast cancer is more found in female patients more than 50 year of age (54%) and patients with post-menopausal status (64%). The risk factors like personal history, family history, proliferative benign breast disease and first child birth after age of 35 years are observed in the present study. Majority of patients are found with invasive type of ductal carcinoma with N1 axillary lymph node involvement (86%) and size of the tumor (T1) between 2 cm to 5 cm (67%). All patients are treated with surgery with adjuvant treatment like Neoadjuvant chemotherapy (41%), Post-Chemotherapy (18%), Biological therapy (15%) and Hormonal therapy (8%). Out of 100 patients, 78% and 92% were Estrogen Receptor positive and Progesterone Receptor positive status. HER-2 positive status is found in 75% which is comparatively high than negative (7%) and unknown (17%) status. In different age group of patient's the disease free survival is more than the recurrence and death. This study highlights the importance of various prognostic factors and hormone receptor status evaluation in different age groups that will aid in therapeutic intervention. This study also determined various treatments, treatment response and survival rate in different age group of breast cancer patients.

Keywords: Breast cancer; Early stage; Prognostic factors; Lymph nodes; Benign breast disease; Axillary node; Estrogen receptors; HER-2 receptors; Progesterone receptors; Risk factors of breast cancer; Treatment of breast cancer

Abbreviations: LABC: Locally Advanced Breast Cancer; ER: Estrogen Receptor; PR: Progesterone Receptor; HER-2: Human Epidermal Receptor-2

Introduction

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast [1]. Breast cancer is the second most common cancer in women in the world. Nearly 1.7 million new breast cancer cases were diagnosed which represented about 12 percent of all new cancer cases and 25 percent of all cancers in women (according to the latest date for available data) [2]. The etiology of breast cancer is unknown but several predisposing risk factors like genetic, endocrine and environmental factors for the disease have been determined. American Joint Committee on Cancer describes the types and stages of breast cancer [3]. Stage 0 indicates noninvasive carcinomas (Lobular carcinoma in situ or ductal carcinoma in situ) and cancer cells have not invaded the surrounding breast tissue. Stage I indicates the tumor is no more than 2 cm in size and cancer cells have not spread beyond the breast.

Stage II indicates either the tumor has spread to the lymph nodes under the arms but the tumor is less than 2 cm in size, or the tumor has not spread to the lymph nodes under the arms but is greater than 5 cm in size, or the tumor is between 2 and 5 cm and may or may not have spread to the nodes. Stage III indicates the tumor is greater than 5 cm in size and has spread to the lymph nodes under the arms. Stage IV indicates the cancer has spread to other parts of the body (metastatic cancer). Breast cancer not spread beyond the breast or the axillary lymph nodes are known as early stages (Stage 0,1,2). According to guideline of National Comprehensive Cancer Network, locally advanced breast cancer (LABC) refers to large breast tumors (> 5 cm) associated with either skin or chest wall involvement or with fixed axillary lymph nodes or with involvement of the ipsilateral internal mammary or supraclavicular nodes (stage III) [4]. Treatments for breast cancer may involve hormone therapy, chemotherapy, a modified or radical mastectomy, or a combination of these [3]. Prognostic factors are capable of providing information on clinical outcome of patient at the time of diagnosis, irrespective of therapy.

Prognostic factors are able to correlate with disease-free or overall survival in the absence of systemic adjuvant therapy and, also with the natural history of the disease. Such markers are usually indicators of growth, invasion, and metastatic potential. Prognostic factors are different from the predictive factors. Predictive factors are factors intend to assess the outcome of patients receiving a

certain systemic therapy and thus are intimately associated with sensitivity or resistance to therapy. Such markers are either within the target of the treatment or serve as modulators or epiphenomena related to expression and/or function of the target [1-6]. Although they can be separately classified, several factors such as hormone receptors (Estrogen receptor, progesterone receptor) and Human epidermal receptor-2 over expression in breast cancer are both prognostic and predictive. Based on this, aim of the present study was to determine prognostic factors analysis of 100 cases of early stage and locally advanced breast cancer.

Methodology

This retrospective study includes case records of 100 female patients visiting (January 2013 to April 2013) Bharat Cancer Hospital and Research Institute, Saroli of Surat district of Gujarat. The data were collected from the record according to inclusion criteria from the already diagnosed cases of breast cancer. Patients age between 30 -70 years, first time diagnosed with primary stage and Locally Advanced of Breast cancer (Stage 0, 1, 2 and 3) and under appropriate treatment were included in the study. Patients with metastatic breast cancer, breast infection and recurrence of primary breast cancer were excluded. Data were collected by specialized case report forms and analyzed for all prognostic characteristics as follow.

Age

- i. Menstrual period such as post-menopausal or pre-menopausal.
- ii. Risk factors-personal history of breast cancer, family history of breast cancer in first-degree relative, BRCA1/BRCA2 Mutation, Proliferative benign breast disease, early menarche, late menopause, null parity, first pregnancy after age 35 years, exogenous hormones (postmenopausal hormone replacement therapy, oral contraceptives), obesity, sedentary lifestyle, dietary factors, radiation, smoking.
- iii. Axillary nodal status includes invasive or non-invasive and also lobular or ductal carcinoma.
- iv. Tumour size and grade.
- v. Therapy include surgical, chemotherapy, hormonal, biological, radiation.
- vi. Hormonal status such as estrogen receptor status, progesterone receptor status, HER2 status that was positive or negative and also includes unknown reason.
- vii. Response and survival rate of therapy such as complete response, partial response, stable disease and progression of disease.

The data collected were subjected to descriptive statistical analysis.

Results

Patient characteristics

A total of 100 case records of breast cancer patients were included in this study. Distribution of patients based on age groups is shown in Figure 1. Out of 100 patients of different age group, 24 patients were between age group

of 30-40, 22 patients were between age group of 40-50, 33 patients were between age group of 50-60, and 21 patients were between age group of 60-70. The maximum number of cases occurred in patient age group of 50-60 years. 46% cases are below age of 50 years, while 54% cases are above age of 50 years. Distribution of patients based on menstrual period is shown in Figure 2. Pre-menopausal and post-menopausal status was 36% and 64% respectively.

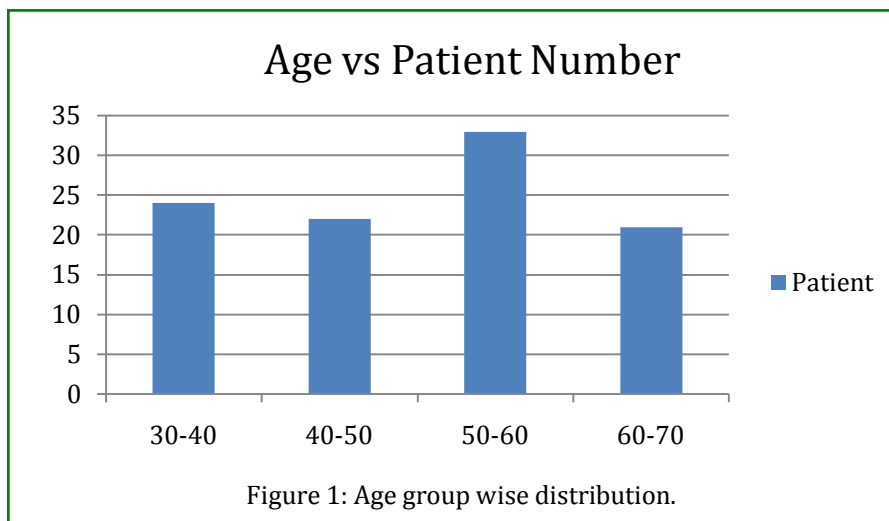


Figure 1: Age group wise distribution.

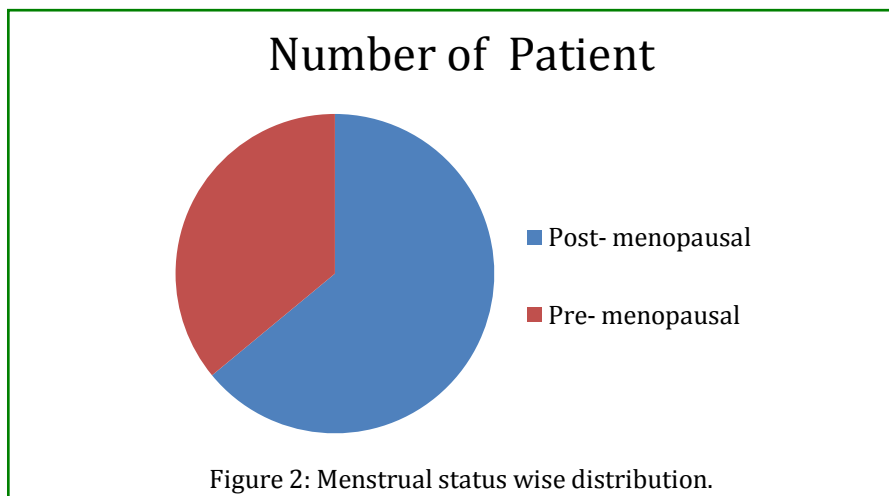


Figure 2: Menstrual status wise distribution.

Epidemiological distribution of risk factors in 100 patients is shown in Figure 3. Dietary factors, smoking, and radiation risk factors are not reported. But, risk factors like personal history of breast cancer, family history; proliferative benign breast disease, early menarche and late menopause, null parity, first pregnancy after age 35 years, exogenous hormones (postmenopausal hormone replacement therapy, oral contraceptives), obesity and sedentary lifestyle are observed in the

present study. The highest risk character observed in all age group was personal history of breast cancer which is highly observed in age between 50 to 60 years. The lowest risk character in all age group is sedentary lifestyle. Family history factor is highly observed in young patient group (30-40 years). In age group between 50-60 years, proliferative benign breast is highly observed as compared to other age groups. Women who gave first child birth after age of 35 elevated breast cancer risk

which is more observed factor in age group 50-60 years. Early menarche and late menopause factor is only

observed in patients age more than 50 years.

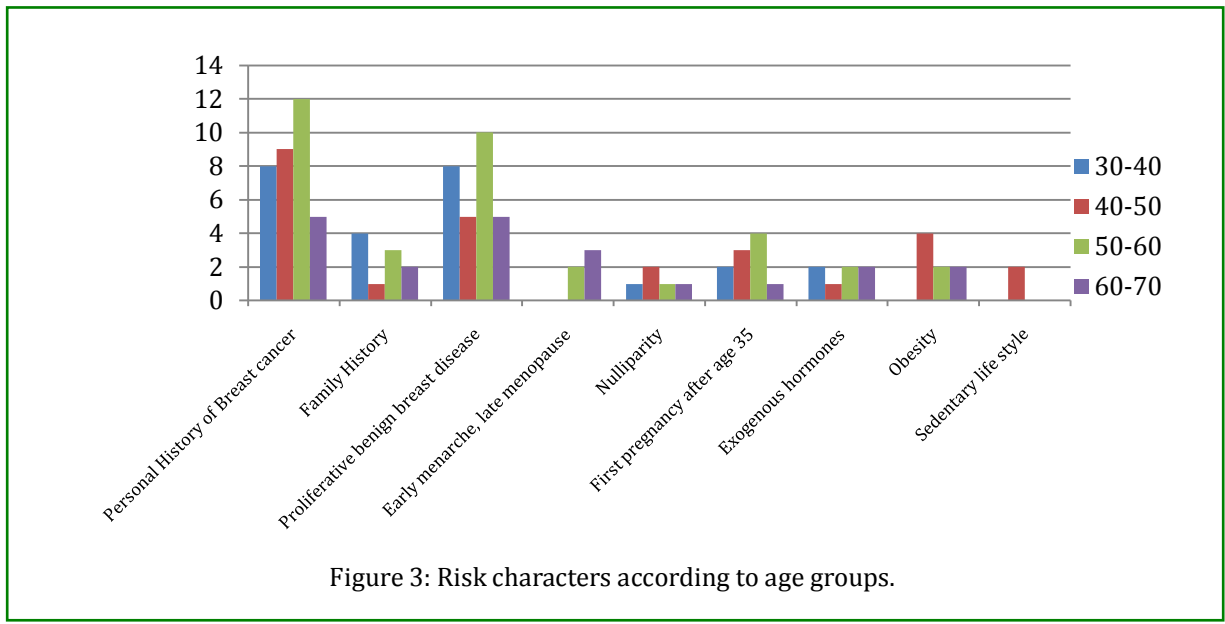


Figure 3: Risk characters according to age groups.

Tumor characteristics

Prognostic factor axillary nodal status distribution is shown in Figure 4. Ductal Invasive carcinoma was observed in all patients of different age groups, except one patient in each age group with noninvasive status (ductal carcinoma in situ). Patients are classified in four nodal groups which are 0 negative nodes (NX), 1-3 cm positive nodes (N0), 4-9 cm positive nodes (N1), and 10 cm or more positive nodes (N2) [7]. In the present study, nodal status N0, N1, N2 percentage are 4%, 86% and 10%

respectively (Figure 5). Axillary lymph node involvement is more in N1 (86%). Figure 6, indicates tumor size distribution of 100 patients. Data shows that 4 patients with no tumor, 19 patients with tumor size between 0-2 cm, 67 patients with 2 to 5 cm tumor size and 10 patients with tumor size more than 5 cm. With TNM (Tumor, node, metastasis) system, stages of breast cancer are classified. Figure 7 shows tumor stage wise epidemiological distribution in various age groups. As shown in Figure 7, tumor stage 2 was highest in the all age group.

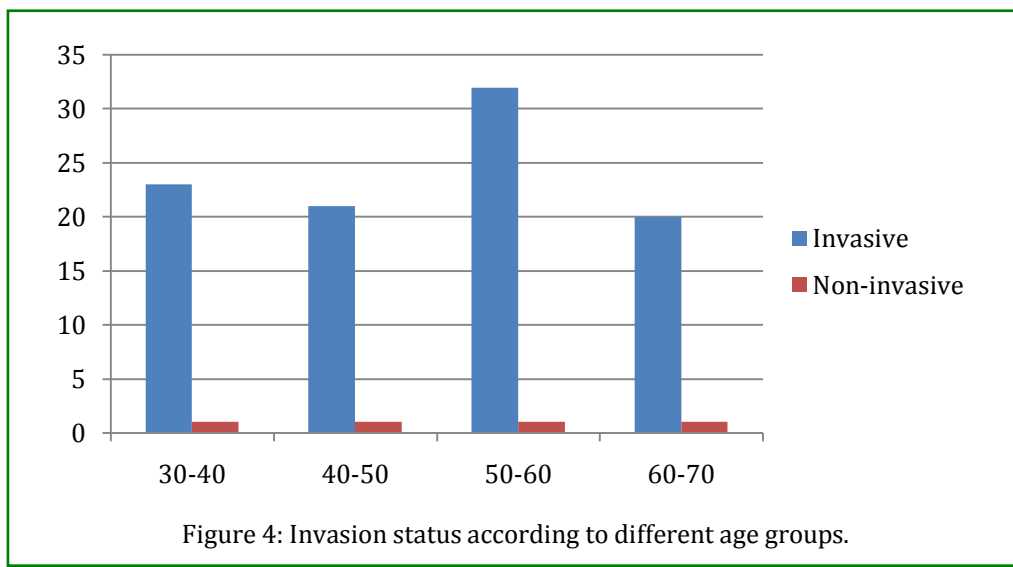
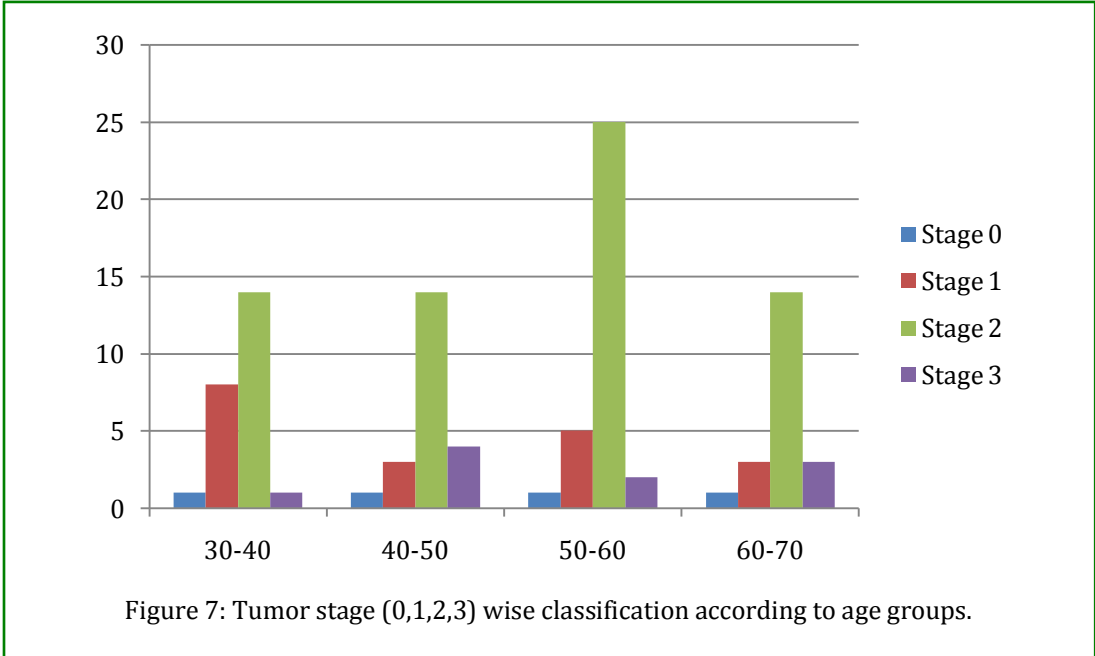
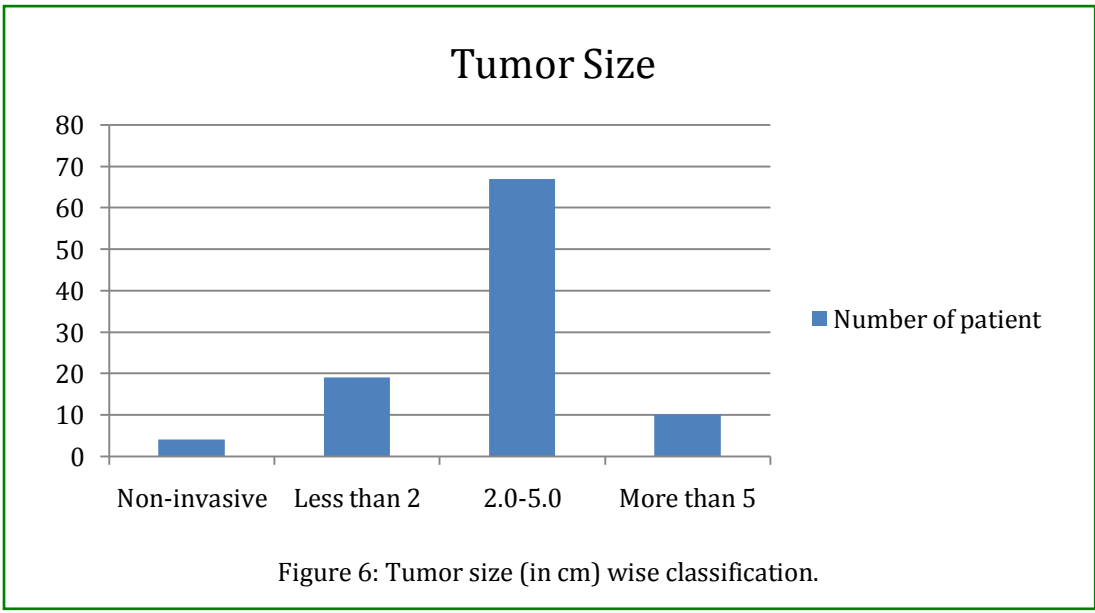
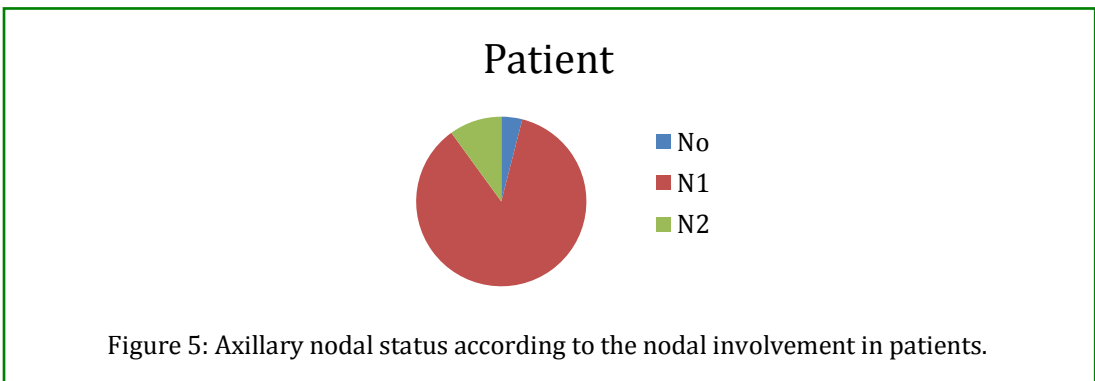


Figure 4: Invasion status according to different age groups.

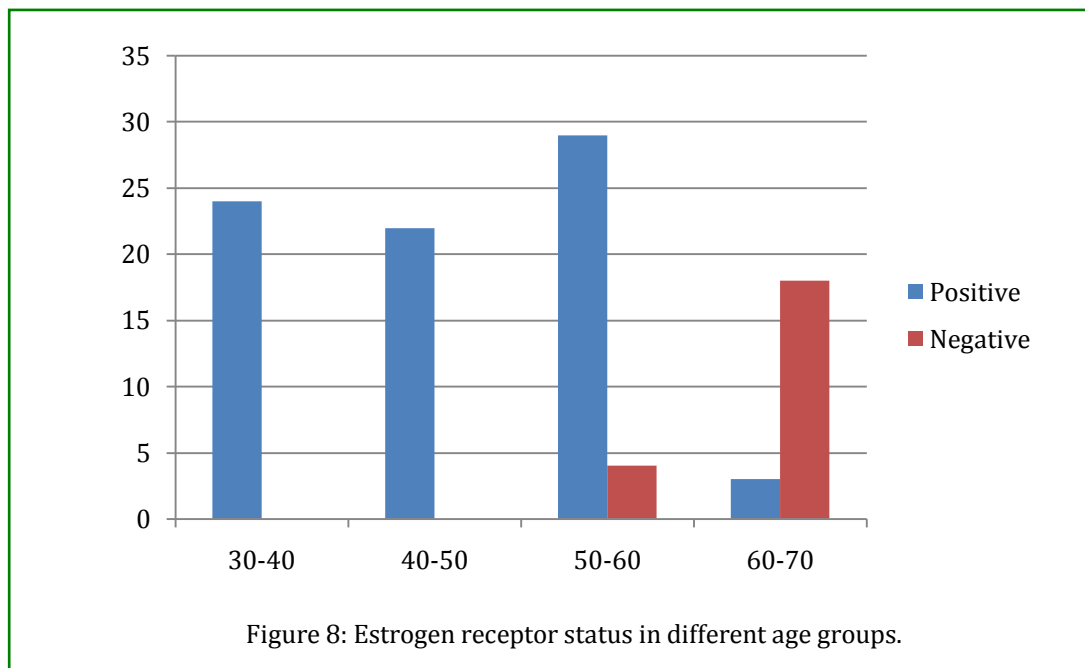


Hormone Receptor Characteristics

Estrogen receptor status

Epidemiological distribution of Estrogen receptor (ER) status in 100 patients of different age group is shown in Figure 8. 78% and 22% patients were ER positive and ER

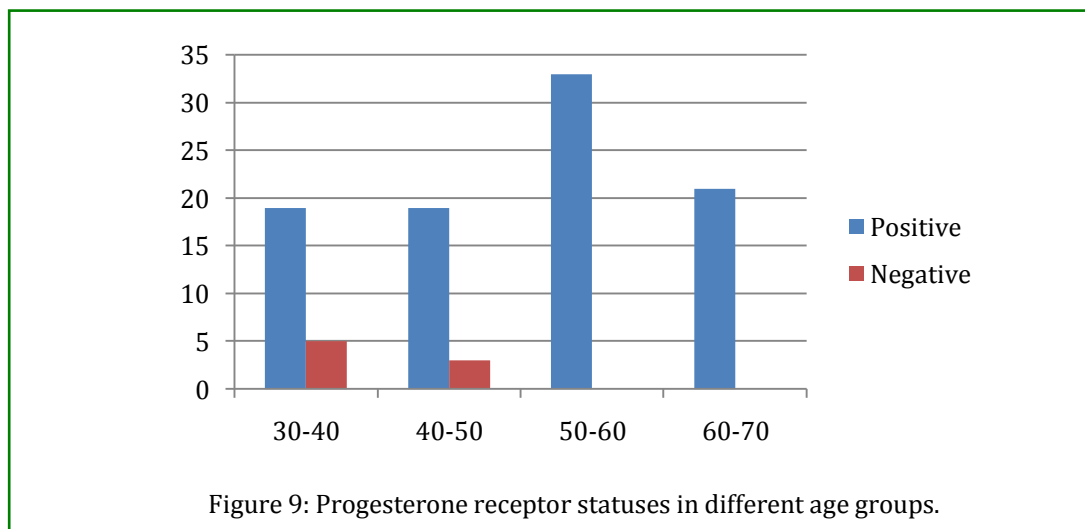
negative respectively. ER positive is observed in all age group (30-40 years-24%, 40-50 years-22%, 50-60 years-29%, 60-70 years-3%). ER positive is highly observed in age group 50-60 years (29%). All patients aged less than 50 years were ER positive. ER negative only observed in patients aged more than 50 years (50-60 years-4%, 60-70 years-18%).



Progesterone receptor status

Epidemiological distribution of Progesterone receptor (PR) status in different age groups is shown in Figure 9. 82% patients were PR positive and 8% were PR negative. PR positive is observed in all age group (30-40 years-

19%, 40-50 years-19%, 50-60 years-33%, 60-70 years-21%). PR positive is highly observed in age group 50-60 years (33%). All patients aged less than 50 years were PR positive. PR negative only observed in patients aged less than 50 years (30-40 years-5%, 40-50 years-3%) (Figure 9).



Human epidermal receptor-2 (HER-2) status

Epidemiological distribution of Human Epidermal Receptor-2 (HER-2) status in different age groups is shown in Figure 10. 75 patients were HER-2 positive (30-40 years-17%, 40-50 years-21%, 50-60 years-28%, 60-70

years-9%). and 8 were HER-2 negative (30-40 years-5%, 40-50 years-0%, 50-60 years-2%, 60-70 years-1%). and 17 patients were showing unknown status (30-40 years-2%, 40-50 years-1%, 50-60 years-3%, 60-70 years-11%). HER-2 positive is highly observed in age group 50-60 years (28%).

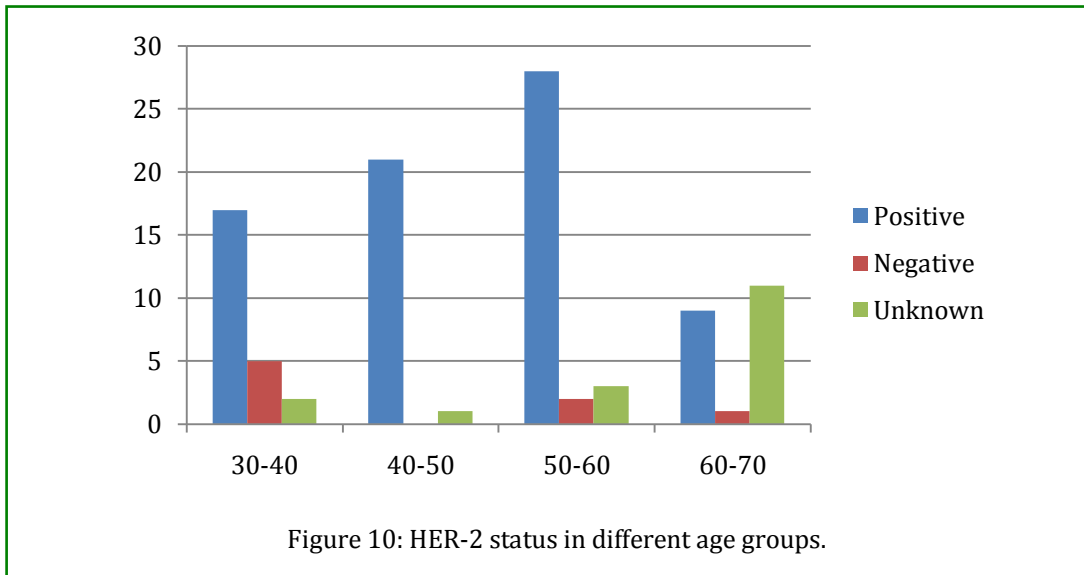


Figure 10: HER-2 status in different age groups.

Therapy given according to age group

Epidemiological distribution of therapy given to different age group is shown in Figure 11. The surgical treatment was given to all 100 patients. Combination of Surgical and neo-adjuvant chemotherapy was highest (41%) in all age

groups followed by Surgical and Post-Chemotherapy (18%), Surgical and Biological therapy (15%) and Surgical and Hormonal therapy (8%). Adjuvant hormonal therapy was given in patients aged less than 50 years and not in the patients aged more than 50 years.

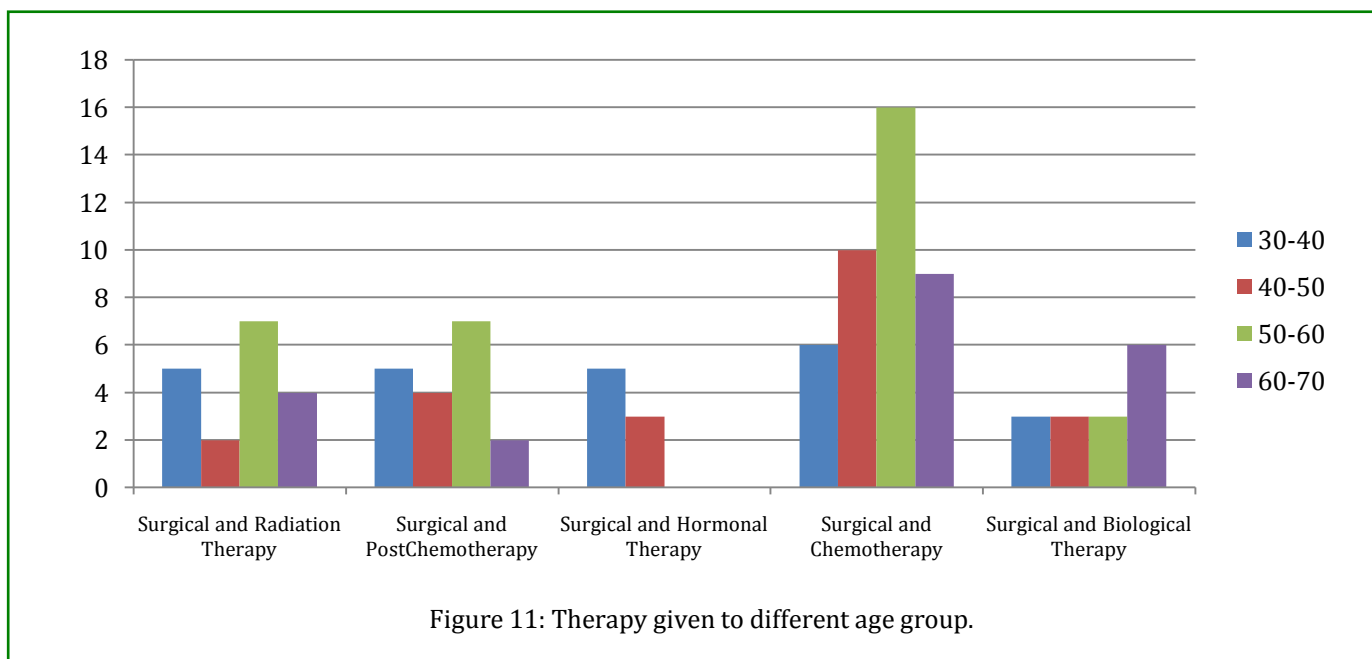
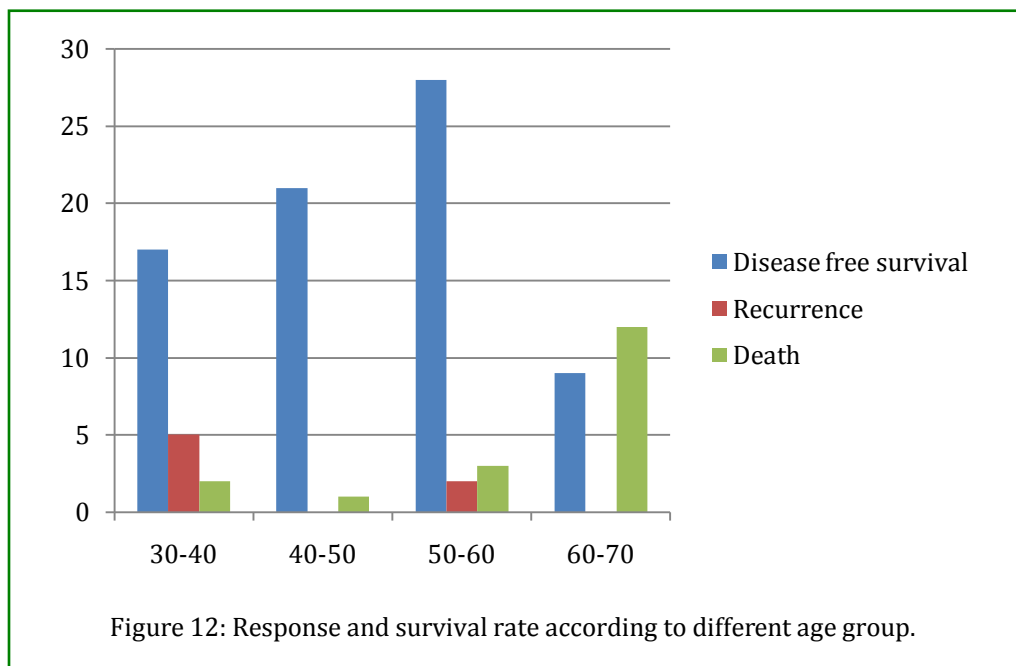


Figure 11: Therapy given to different age group.

Response and survival rate of therapy

Response and survival rate of therapy in different age groups of 100 patients are shown in Figure 12. Disease free survival after surgery and other treatment was

observed more in all age groups (in total 75 patients) than recurrence (in total 7 patients) and death (in total 18 patients). Death is more observed in age group 60-70 years which may be age related.



Discussion

Breast cancer is the most common cancer among urban women and second most common among rural women in India [8]. Many prognostic factors such as patient factors, stage of disease, tumor biology, and cancer treatment influence the survival of patients. Age is known to be an important factor that determines the prognosis. The maximum number of cases (33%) reported in the present study are between the age of 50 to 60 years which is similar as per official statistical data of India, maximum number of cases in India between age group of 50-60 years (30%). In the present study, 46% cases are below age of 50 years, while 54% cases are above age of 50 years. Similar results are observed in India statistical data (48% below age 50 years and 52% above age 50 years) [8]. Other research studies also observed occurrence of breast cancer in old female more than young [9-12]. In the present study, breast cancer is more observed in post-menopausal females which can correlate with our result of more incidence of breast cancer in old age groups [12].

In the present study, dietary factors, smoking, and radiation risk factors are not observed in our study. But, personal history of breast cancer, family history, proliferative benign breast disease, first pregnancy after age 35 year are the major risk factors present in our

study. Also reported late pregnancy after 35 years, family history of breast cancer, benign mammary disease history as risk factors [13]. Ductal invasive carcinoma which is observed in the present study is most common type of breast cancer [3]. Nodal status is the most powerful independent prognostic factor in breast cancer [1]. There is evidence that overall survival decreases as the number of positive nodes increases [14]. Furthermore, there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence [15]. In the present study nodal status N0, N1, N2 percentage are respectively 4%, 86% and 10% so axillary lymph node involvement is more in N1 (86%) [16]. Reported similar result with highest N1 (55%) among 60 number of patients and the rest N0 and N2 are respectively 23.67% and 21.33%.

These data demonstrate that the risk of recurrence is significant enough with lymph node positive disease to warrant adjuvant systemic therapy. Small tumors confined to the breast, without micro-metastasis have high chances of cure whereas big tumours which spread to axillary lymph nodes are consistently associated with subclinical systemic spread and strongly predict advanced disease [17]. Thus, tumour size reflecting how long the tumour present has significant prognostic implications. In the present study 86% patients are found with tumor size

more than 2 and less than 5 cm are in T1 of stage 2. Similar findings are also observed in other reported Indian studies [18,19]. Estrogen regulates the differentiation and proliferation of breast epithelial cells and interacts with the estrogen receptor (ER) in the nucleus.

Prolonged exposure of estrogen is an important risk factor for cancer. Progesterone receptor (PR) expression in normal breast epithelium is regulated by ER [20]. The HER2/neu or c-erbB-2 receptor is a 1255 amino acid, 185 kD trans membrane glycoprotein located at the long arm of human chromosome 17 (17q12) with intrinsic tyrosine kinase activity homologous to the epidermal growth factor receptor [21]. It is amplified and/or over expressed in approximately 30% of human breast tumors. HER2 over expression is associated with a more aggressive disease, higher recurrence rate, and shortened survival [22]. Presence of Estrogen receptor (ER), Progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) status in invasive breast carcinoma is now-a-days routinely estimated as these markers are considered to be important prognostic factors [23]. In the present study, 78% and 22% patients were ER positive and ER negative respectively while 82% and 8% patients were PR positive and PR negative respectively. This result is similar to study of Kerala state of India [24]. But contrast to other reported Indian studies in which very less ER positive and PR positive reported [25,26]. Women with ER and PR status positive tumor have better prognosis than women with ER and PR negative. The presence of estrogen or progesterone receptors is, however, a powerful predictive factor for the likelihood of benefit from adjuvant tamoxifen.

In the present study, HER-2 positive was 75% followed by unknown 17% and negative status 8% [28]. Study reported positive, and negative HER-2 status as 19.99% and 81.81% and 27 patient unknown HER-2 status out of 60 patients. As such retrospective studies have suggested that HER2 status over expression may also have a predictive role for response to chemotherapy and endocrine therapy. Over expression is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality in node-positive patients, while the influence in node-negative patients is more variable [28-31]. It is now well established that adjuvant systemic therapy improves survival in patients with early-stage breast cancer [32,33]. In women with a tumor that has adverse features predicting early recurrence (i.e. lymph node positivity, large size, high grade) adjuvant systemic chemotherapy or hormonal or biological therapy is given to reduce the risk of relapse. Systemic therapies are potentially toxic, however, and identifying the individual patients who are at high risk

and likely to benefit remains a major challenge. In the present study, all patients are treated with surgery with adjuvant treatment like neoadjuvant chemotherapy (41%), post-chemotherapy (18%), biological therapy (15%) and hormonal therapy (8%). Hormonal therapy was nil in the age group of 50-60 years and 60-70 years. Neoadjuvant chemotherapy has emerged as a powerful treatment modality with individualized prognostic significance based on response to therapy [34]. The recurrence was seen in the age group of 30-40 years and 50-60 years whereas the death was more in the age group of 60-70 years compared to the another three age groups. In the present study disease free survival is more but we cannot predict the overall survival due to short duration of study.

Conclusion

All the prognostic factors and hormonal receptor status were identified and evaluated in different age group of patients. This study also determined various treatments, treatment response and survival rate in different age group of breast cancer patients.

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