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Original Article

Surgery Section

Assessment of Clinicopathological Profile and Receptor Status of Breast Cancer Patients at a Tertiary Care Centre in Uttarakhand, India: A Prospective Cohort Study

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ABSTRACT

Introduction: Breast carcinoma has become a major public health problem among both urban and rural populations in India. The management of breast carcinoma depends on hormone receptor status and the pathological properties of the tissue, which serve as important prognostic markers.

Aim: The aim of this study was to analyse the clinicopathological parameters and receptor status in breast cancer patients in the Garhwal Region of Uttarakhand.

Materials and Methods: This prospective cohort study involved 51 patients who underwent modified radical mastectomy for breast carcinoma at the Department of General Surgery, Government Doon Medical College, Dehradun, Uttarakhand, India. The study was conducted over a period of two years and seven months, from May 2018 to December 2020. Various parameters such as age, side and quadrant of breast involvement, TNM stage, histological grade, receptor status, molecular subtypes, and axillary lymph node status were evaluated. The data was tabulated using Microsoft Excel 2007. The distribution of various receptors in tumour specimens was compared with clinicopathological variables and expressed as percentages.

Results: The mean age of the study participants was 52.54±13.24 years, with a male to female ratio of 2:98. In this study, the majority of females (62.74%) belonged to the age group of 40 to 60 years. Left breast carcinoma showed a slightly higher prevalence (52.94%) than right breast carcinoma (47.05%), and the upper outer quadrant was the most commonly involved (50.98%). Infiltrating ductal carcinoma, not otherwise specified, was the most common histological type observed in all patients. The majority of patients (84.31%) had tumour sizes less than 5 cm. Grade-II tumours were the most frequent grade, observed in 34 cases (66.66%). Among the tumour stages, T2 stage accounted for the highest frequency (67%), followed by T3. The authors found that the highest frequency of tumours belonged to N0 stage (29.41%), followed by N1, N2, and N3, respectively. The corresponding rates of luminal A, luminal B, triple-negative, and Human Epidermal Growth Factor Receptor 2 (HER-2)/neu enriched subtypes were 5 (14.7%), 3 (8.82%), 11 (32.5%), and 3 (8.82%), respectively. The cases negative for Oestrogen Receptor (ER) and Progesterone Receptor (PR) were found to have high-grade disease on histological evaluation.

Conclusion: The higher percentage of Grade-II and III tumours observed in this study highlights the need to increase health awareness in this area in order to decrease morbidity and mortality. The study recommends that Immunohistochemistry (IHC) classification serves as an important prognostic factor in breast cancer patients.

Keywords: Her 2 neu, Oestrogen receptor, Progesterone receptor, Triple-negative breast cancer, Tumour stage, Tumour grade

INTRODUCTION

Breast cancer is the most common cancer in urban Indian females and the second most common in rural Indian women. It has been observed that over several decades, the incidence of breast carcinoma has increased while the death rate has decreased. Tumour size and lymph node metastasis have been identified as the most powerful prognostic factors in breast cancer patients [1,2]. Several researchers have evaluated that an increasing tumour size is associated with a higher number of metastatic lymph nodes [3-5]. Importantly, the absence of lymph node involvement is significantly associated with a better prognosis. Numerous studies have shown that breast cancer in younger age groups tends to be more advanced and aggressive compared to older age groups [6-8]. Additionally, breast tumours in younger age groups are more likely to be of higher grade, hormone receptor-negative, poorly differentiated, aneuploid, exhibit a greater extent of lymphovascular invasion, and have overexpression of HER-2 compared to breast tumours in older age groups [6,9]. Breast cancer has long been recognised as an endocrine-related cancer since Beatson demonstrated that tumours regressed after oophorectomy in advanced breast cancer patients [9]. Tumours that are Oestrogen Receptor (ER) and Progesterone Receptor (PR) positive have a lower risk of mortality compared to tumours that are ER and/or PR-negative. The ER and PR status, as well as HER-2/neu expression, are used to determine treatment strategies for breast cancer patients due to their prognostic value and response to Endocrine Therapy (ET) [10]. Four subtypes of breast cancer have been identified through biomolecular diagnosis: luminal A, luminal B, HER-2/neu overexpressed, and Triple-negative Breast Cancer (TNBC) [11].

The present study was conducted to determine the steroid receptor status of breast tumours in women in this hilly state of North India. The study examined the clinical parameters, morphological profile, and hormone receptor status in breast cancer patients.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of General Surgery at Government Doon Medical College, Dehradun, Uttarakhand, India from May 2018 to December 2020. The study involved 51 patients with breast cancer who were diagnosed and underwent surgery in the Department of General Surgery over a period of two years and seven months.

Inclusion criteria: All patients admitted with breast carcinoma to the Department of Surgery at Government Doon Medical College and Hospital from May 2018 to December 2020 were included in the study. All consecutive primary operable cases were included.

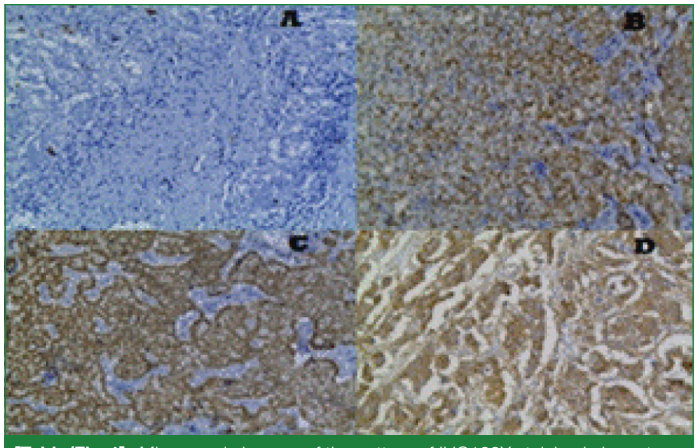
Exclusion criteria: In-situ lesions, recurrences, sarcomas, benign and secondary lesions, patients with distant metastatic disease, and cases treated with neoadjuvant therapy were excluded from the study.

Study Procedure

The status of ER and PR was determined solely based on immunohistochemical staining using standard techniques. ER or PR was considered positive if 1% or more of tumour cell nuclei showed immunoreactivity. All patients in the study group underwent modified radical mastectomy with axillary dissection. Mastectomy specimens were fixed in formalin, and histopathological examination of paraffin-embedded tissues was performed after staining with haematoxylin and eosin. The parameters recorded included age, side and quadrant of the involved breast, TNM stage, histological grade, receptor status, molecular subtypes, and axillary lymph node status. The expression of ER, PR, and HER-2/neu was analysed in the received specimens from modified radical mastectomy and interpreted based on the American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations 2013 [12].

For Immunohistochemistry (IHC), sections were cut serially at 5 µm for routine haematoxylin and eosin staining and IHC analysis. The Ultra View™ (Ventana Medical Systems, Inc. Tucson, AZ, USA) universal Diaminobenzidine (DAB) detection kit, a biotin-free, multimer-based detection system for specific and sensitive detection of mouse IgG, mouse IgM, and rabbit IgG primary antibodies, was used. Counterstaining with blueing reagent and post-counter staining took four minutes each. After staining, the sections were dehydrated in ethanol, cleared in xylene, and covered with Mountex and cover slips.

The anti-ER and anti-PR antibodies directly reacted with human ER and PR proteins located in the nuclei [Table/Fig-1]. The ER and PR results were manually screened and interpreted as positive or negative based on scores for proportion and intensity. ER and PR expression were scored between 0 and 8 as follows: 0 (negative)-no nuclei staining; 1 (borderline)-1% of nuclei staining; 2 (positive)-1-10% of nuclei staining; 3 (positive)-11-33%; 4 (positive)-34-66%; 5, 6, and 7 (positive)-100% of nuclei staining [13]. HER-2/neu expression was scored from 0 to 3 as follows: 0 (negative)-no membranous staining identified; 1 (negative)-faint staining involving 10% of positive cells; 2 (positive)-weak but definitive staining of the membrane over at least 10% of positive cells; 3 (positive)-strong positive staining of the complete membrane in more than 20% of cells.



[Table/Fig-1]: Microscopic images of the pattern of IHC100X staining in breast carcinoma; a) Negative expression of receptors (ER, PR & HER-2/neu); b) Nuclear stain of ER; c) Nuclear stain of PR; d) Cytoplasmic stains of HER-2/neu.

Histopathological tumour grading was performed using the Elston and Ellis modification of the Scarff Bloom Richardson scoring (Elston and Ellis, 1991). The Modified Bloom Richardson-Elston (MRB) grading system was obtained by adding up the scores for tubule formation, nuclear pleomorphism, and mitotic count [14]. Each criterion was assigned 1, 2, or 3 points, resulting in a total score ranging from three to nine. The final grading was as follows:

1) 3 to 5 points-Grade-I

2) 6 to 7 points-Grade-II

3) 8 to 9 points-Grade-III

TNM staging was conducted according to the American Joint Committee on Cancer (AJCC) 7th edition [15].

STATISTICAL ANALYSIS

The data was tabulated and analysed in Microsoft Excel 2007. The distribution of various receptors (ER, PR, and HER-2neu) in tumour specimens from 34 patients was compared with various clinicopathological variables, such as age, tumour size, tumour grade, TNM stage, and Lympho Vascular Space Invasion (LVSI). The distribution of various receptors in tumour specimens was tabulated as percentages to categorise the receptors based on their immunohistochemical status.

RESULTS

A total of 51 patients were included in the study, and all patients underwent modified radical mastectomy. The study group included only one male patient, resulting in a male-to-female ratio of 2:98. The mean age was 52.54±13.24 years. The youngest patient was 29 years old, and the oldest patient was 78 years old. Most of the patients (32 out of 51; 62.74%) were in the age group of 40 to 60 years, 12 patients (23.52%) were older than 60 years, and seven patients (13.72%) were less than 40 years of age [Table/Fig-2]. The majority of the patients (44 out of 51; 86.27%) belonged to the Hindu religion, five patients (9.8%) were Muslim, one patient (1.96%) was Sikh, and only one patient (1.96%) belonged to the Christian religion. In the present study, left breast carcinoma showed slightly greater prevalence (27 out of 51; 52.94%) than right breast carcinoma (24 out of 51; 47.05%) [Table/Fig-3]. The upper outer quadrant was the most commonly involved (26 out of 51; 50.98%). The central quadrant was involved in 13 patients (25.49%), the upper inner quadrant of the breast was involved in 14 patients (27.45%), the lower outer quadrant was involved in 11 patients (21.56%), the lower inner quadrant was involved in eight patients (15.68%), and more than one quadrant was involved in 21 patients (41.17%) [Table/Fig-3]. The mean size of the lesion was 3.43 cm, ranging from 0.6 cm to 8.5 cm. The majority of the patients (43 out of 51; 84.31%) had a tumour size less than 5 cm [Table/Fig-4].

Age in years	No. of patients	Percentage (%)
<40	7	13.72
40-60	32	62.74
>60	12	23.51

[Table/Fig-2]: Age wise distribution of patients (n=51).

Parameters	Variables	No. of patients	Percentage (%)
Breast involved	Right	24	47.05
	Left	27	52.94
Quadrant involved	Central	13	25.49
	Upper outer quadrant	26	50.98
	Upper inner quadrant	14	27.45
	Lower outer quadrant	11	21.56
	Lower inner quadrant	8	15.68
	More than one quadrant	21	41.17

[Table/Fig-3]: Side-wise and quadrant-wise distribution of patients.

Age in years	Size in centimetres (cm)	
	Less than 5 cm	More than 5 cm
<40	6	1
40-60	26	6
>60	11	1
Total	43	8
Percentage	84.31%	15.68%

[Table/Fig-4]: Size of tumour and its relation with age.

Invasive ductal carcinoma of no special type was seen in all patients. Invasive ductal carcinoma with medullary features was histologically observed in only one patient. According to MRB Grading, four cases (7.84%) were Grade-I, 34 cases (66.66%) were Grade-II, and 13 cases (25.49%) were Grade-III [Table/Fig-5].

Histological grade of tumour	No. of patients (n)	Percentage (%)
Grade-I	4	7.84
Grade-II	34	66.66
Grade-III	13	25.49

[Table/Fig-5]: Histological grade of the patients [14].

The ER and PR status were available in 34 patients, and the Her-2/neu receptor status was available in 27 patients only. Eleven cases (32.35%) were ER-positive, 10 cases (29.41%) were PR-positive, and eight cases (23.52%) were Her-2/neu positive. A total of 23 cases (67.64%) were ER-negative, 24 cases (70.58%) were PR-negative, and 16 cases (47.05%) were Her-2/neu negative, while three cases (8.82%) showed a Her-2/neu equivocal result [Table/Fig-6]. The corresponding rates of ER+/PR+/Her-2/neu- (Luminal A), ER+/PR-/Her-2/neu+ (Luminal B), ER+/PR+/Her-2/neu+, triple negative, and HER-2/neu enriched (ER-/PR-/HER-2+) subtypes were 14.7%, 8.82%, 11.76%, 32.35%, and 8.82%, respectively [Table/Fig-6,7].

Variables		ER+	ER-	PR+	PR-	Her-2/neu+	Her-2/neu-	Her-2/neu equivocal
Age (years)	<40	1	3	1	3	1	2	1
	40-60	8	13	6	14	5	8	1
	>60	2	7	3	7	2	6	1
Tumour size (Cm)	<5	9	18	9	19	5	13	3
	>5	2	5	1	5	3	3	
pT stage	T1	2	5	2	6	4	3	
	T2	8	14	8	14	3	12	
	T3	1	2	0	2	2	2	
	T4	0	2	0	2	0	1	
pN stage	N0	5	11	4	11	5	5	
	N1	3	5	2	6	3	6	
	N2	0	6	1	6	2	2	
	N3	3	1	3	1	1	3	
TNM stage [15]	IA	1	3	0	4	2	1	
	IIA	4	9	4	9	3	5	1
	IIB	2	1	2	1	0	2	1
	IIIA	1	7	1	7	2	4	1
	IIIB	0	2	0	2	0	1	0
	IIIC	3	1	3	1	1	3	0

[Table/Fig-6]: Distribution of study variables according to receptor status.

Out of these 51 patients, 15 (29.41%) had no lymph nodes positive for carcinoma metastasis in the histopathology specimen. In 14 (27.45%) patients, 1-3 lymph nodes were positive. In 10 (19.60%) patients, 4-9 lymph nodes were positive, and eight (15.68%) patients had more than 10 lymph nodes positive in the final specimen [Table/Fig-8].

Receptor status	No. of patients (n)	Frequency
ER+/PR+/HER-2- (Luminal A)	5	14.7%
ER+/PR-/HER-2+(Luminal B)	3	8.82%
ER+/PR+/HER-2+	4	11.76%
ER-/PR-/HER-2+(Her 2/neu enriched)	3	8.82%
ER-/PR-/HER-2- (Triple Negative)	11	32.35%
ER-/PR-	6	17.64%
Others	5	14.7%

[Table/Fig-7]: Distribution of patients according to molecular subtypes.

Lymph nodes showing metastasis	No. of patients (n)	Percentage (%)
N0	15	29.41
N1	14	27.45
N2	10	19.60
N3	08	15.68

[Table/Fig-8]: Axillary lymph node status.

DISCUSSION

In the present study, the majority of cases (32 out of 51; 62.74%) were in the age group of 40 to 60 years, with a mean age of 52.54 years. Chow LW et al., conducted a study in Hong Kong where the mean age of patients was 56.6 years (range, 20-98 years) [16]. Gupta P et al., reviewed breast cancer patients in the Jaipur region and found that the most common age group was 45-54 years [17]. However, in developed countries, the mean age of breast cancer patients is almost one decade higher compared to Indian studies [18,19]. In India, the majority of breast carcinomas are diagnosed at an advanced stage due to lack of awareness and absence of a breast cancer screening program. Delayed presentation may be related to a rural background and lack of education. The youngest patient in our study was 29 years old, and the oldest patient was 78 years old, which aligns with the study conducted by Amit M et al., [20]. In our study, the prevalence of male breast cancer was found to be 2%. Weiss JR et al.,'s study on the epidemiology of male breast cancer concluded that it is a rare disease, accounting for approximately 1% of all breast cancer cases [21]. Similar findings were noted in another study conducted by Joseph A and Mokbel K [22].

It has been observed that left breast carcinoma shows a slightly greater prevalence than right breast carcinoma, and the upper outer quadrant of the breast is most commonly involved, as seen in various reports [23,24]. Possible explanations include the fact that the left breast is bulkier and the upper outer quadrant has a relatively larger volume of breast tissue [25]. Invasive ductal carcinoma of no special type was the most common histological type of breast cancer in the present study. A clinical database study conducted by Wang LW et al., reported that the highest numbers of cases were in the 45-49-year age group and had invasive ductal carcinoma, accounting for 19.1% (480/2,525) and 81.0% (1,982/2,446) respectively [26]. According to the Nottingham Modified Bloom-Richardson System score, most of the tumours were Grade II (n=34, 66.66%), followed by Grade III (n=13, 25.49%) and Grade I (n=4, 7.84%). This is analogous to the study conducted by Ayadi L et al., who found that the majority of tumours were Grade II (n=33, 46.47%), followed by Grade III (n=24, 33.8%), and then Grade I (n=14, 19.71%) [27]. Estimation of ER, PR, and HER-2/neu is well-established in breast cancer patients as significant prognostic factors for adjuvant hormone therapy.

In the present study, ER and PR status were available for 34 patients, while Her-2/neu receptor status was available for only 27 patients. The authors found that ER was expressed in 32.35% of cases, PR in 29.41% of cases, and HER-2/neu in only 23.58% of cases. In a study conducted by Kaul R et al., on the hormone receptor status of breast cancer in the Himalayan region of northern

India, it was found that on immunohistochemical staining, 34.5% of cases were ER-positive and 36.4% of cases were PR-positive [28]. Hormonal receptor status has shown that the overall positivity rate for ER and PR is lower in India compared to Western literature. In the European and American population, 60-80% of patients were found to have positive receptor expression [29]. This may be due to a lower average age at diagnosis or racial differences.

According to the AJCC TNM staging criteria, the tumour size ranged from 0.6 cm to 8.5 cm, with a mean size of 3.43 cm. The majority of tumours (67%) belonged to the T2 stage (2.0 to 5.0 cm), followed by the T3 stage (more than 5 cm). Similar results were found in various other studies [30]. In the present study, the highest frequency of tumours belonged to the N0 stage (29.41%), followed by the N1 stage (27.45%), N2 stage (19.60%), and N3 stage (15.68%). Other studies have also shown N0 as the most common stage, followed by N1, N2, and N3, respectively [26,30].

In the present study, the authors found lymphovascular invasion in 45.09% of cases. A study by Song YJ et al., reported 54.2% of Modified Radical Mastectomy (MRM) cases, indicating that the maximum percentage of breast carcinoma had lymphovascular invasion, similar to the present study's results [31].

Triple-negative Breast Cancer (TNBC) is defined as a group of breast carcinomas that are negative for ER, PR, and HER-2/neu. In the present study, 11 patients (32.52%) were found to have triple-negative receptor status. All 11 cases were infiltrating ductal type carcinomas, and all of them were Grade II or III. The majority of these cases were found in the 40-60 years age group. Triple-negative breast cancers in the Asian population were associated with a younger age of onset, increasing tumour size, increased prevalence of axillary lymph nodal involvement, higher histological grade of the tumour, and poor prognosis (Ma KK et al., 2013; Li CY et al., 2014) [32,33].

A study conducted by Iwase H et al., analysed data from 14,748 cases registered with the Japanese Breast Cancer Society in 2004. It showed that among the cases examined for ER, PgR, and HER-2, the hormone-responsive subtype with ER positive/PgR positive/ HER-2 negative was the most common (53.8%), followed by the TN subtype (15.5%) [34]. Another seven-year retrospective study of 1134 invasive breast cancer subjects conducted by Onitilo AA et al., compared clinicopathologic features and survival based on breast cancer subtypes defined by ER/PR and HER-2 expression. The study concluded that ER/PR-, HER-2- subtype had the worst overall survival {hazard ratio, 1.8; 95% Confidence Interval (CI), 1.06-3.2} and the worst disease-free survival (hazard ratio, 1.5; 95% CI, 0.8-3.0) [35].

In the present study, it was found that TNBC has poor prognostic characteristics compared to other subtypes of breast cancer. Although patients with TNBC tend to have a poor prognosis, only chemotherapy is expected to be effective because no therapeutic targets have been established yet. The authors of the present study did not find any significant association between the expression of ER/PR and lymph node metastasis. Similar results have been documented in other studies [36].

Limitation(s)

In the present study, the triple-negative receptor status was not analysed in all the patients. The study was conducted in a single institute, resulting in a small sample size. Additionally, the triple-negative receptor status was not analysed in all the patients.

CONCLUSION(S)

Most of the patients were in the middle-age group, and the upper outer quadrant of the breast was more commonly involved. The present study confirms that invasive ductal carcinoma, No Special Type (NST), was the most common form of histological breast cancer. The percentage of ER and PR expressing breast tumours is lower compared to that documented in Western countries. However, the triple-negative receptor status was not analysed in all the patients. The presence of a large number of Grade-II and III patients in the present study highlights the need to increase health awareness in the area to reduce morbidity and mortality. Furthermore, the present study recommends that IHC classification is an important clinical tool at a reasonable cost, which aids in making therapeutic decisions and serves as an important prognostic factor in breast cancer patients.

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