HORMONE RECEPTOR STATUS (ER, PR) IN BREAST CARCINOMA: CORRELATION WITH CLINICOPATHOLOGICAL AND PROGNOSTIC PARAMETERS

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ABSTRACT: Objectives: To study ER and PR status in breast carcinoma in the study sample and to correlate ER and PR status with clinicopathological prognostic parameters.

Materials and Methods: All the breast cancer specimens (mastectomy and lumpectomy specimens) sent to Department of pathology, Al-Ameen Medical College, Vijayapur for histopathological study during the period of 3 years (June 2013-May 2016) were included in the study. Clinical data were obtained from hospital records. The specimens were examined for gross details, routinely processed and stained with H & E stain and were examined for presence of breast carcinoma. Assessment of various clinical and histologic prognostic parameters was done. All these cases were subjected to IHC for ER and PR status.

Results: Out of 108 cases, 58 cases were positive for both ER & PR, 35 cases were negative for both ER & PR, 12 cases were positive for ER and negative for PR and only 3 cases were negative for ER and positive for PR. There was significant correlation of histological type, grade and tumor differentiation with ER, PR status. There was no significant correlation between age of the patient and necrosis with ER, PR status.

Conclusion: High grade tumors are more likely to be ER, PR negative and such patients are not likely to respond to hormonal therapy as compared to patients with low grade tumors.

Keywords: *Immunohistochemistry; Estrogen receptor; Progesterone receptor*.

INTRODUCTION:

Breast cancer is the commonest cancer in urban Indian females, and the second commonest cancer in the rural Indian women. In India, breast cancer is second to cancer of the cervix among women, but is considered the leading cancer in certain metro cities. Estrogen and progesterone receptors (ER, PR) and more recently, Her-2/neu have with increasing importance influenced the management of the malignancy.[1]

There are increasing trends of breast cancer in India according to the various Registries of National Cancer–Registry Project. India accounts for nearly 6% of deaths due to breast cancers in the world and also one out of every 22 women in India is diagnosed with breast cancer every year. In India breast cancer rate is more in younger women when compared to other parts of the world where there is more breast cancer in postmenopausal age group.[2]

It is of serious concern owing to the rising incidence of the breast cancer in the last 5-10 years. Women diagnosed with breast cancer have relative survival rates of 96%, 79%, 67% and 60% for 1, 5, 10 and 15 years respectively.[3] Estrogen receptor is a regulator of mammary epithelial growth, proliferation and differentiation whose complex cellular interactions are mediated by a magnitude of ligands, cofactors and other stimuli.[4, 5]

A crucial development in the treatment of breast carcinoma has been the realization that the presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy[6]

Hormone receptor status should be defined in all newly diagnosed, invasive breast carcinomas as well as in recurrences, in order to determine patient eligibility for hormone therapy, which provides substantial survival benefit for patients with hormone positive tumors. Accurate determination of ER and PR status is, therefore, critical for ensuring that patients receive appropriate therapy.[7, 8]
The use of immunohistochemistry (IHC) to assess the estrogen receptor (ER) status of breast cancer in formalin fixed and paraffin embedded sections is now a routine practice worldwide. ER status as determined by IHC analysis has been shown to be a prognostic factor for patients with breast cancer.[4]

The estrogen receptor (ER) is a steroid hormone receptor that resides in the cytoplasm and participates in cell proliferation, survival, and invasion in ER positive breast cancer. The binding of estrogen is essential for translocation of the ER from the cytoplasm to the nucleus, where estrogen-bound ER dimerizes and binds to the estrogen response elements of target genes for the activation of gene expression. ER, as a transcription factor, also interacts with co-regulatory proteins and other transcription factors. In addition, another form of ER, a membrane-bound or cytoplasmic protein, has non-genomic action.[9, 10]

For instance, ER positive (ER+) tumors are more responsive to hormonal therapies than ER negative (ER-) tumors. Major aim of determining the ER receptor status is to assess predictive response to hormonal therapy. It is proven that chemotherapy and hormonal therapy improves the prognosis of post operation breast cancer.[11]
The significance of PR status has been studied to determine its predictive role in breast cancer treatment and its role as a prognostic factor. There are some evidences to suggest that the joint classification of ER and PR status enhances the predictive power compared with either one separately.[12]

Aims and objectives:
1. To study the ER and PR status in breast carcinoma in the study sample.
2. To correlate ER and PR status with clinicopathological prognostic parameters

METHODS:
All the mastectomy specimens of breast carcinoma submitted to the Department of Pathology, AMCH, Vijayapur for histopathological study during the period from June 2013- May 2016 (3years).
Clinical data were obtained from hospital records and requisition forms received in the department. On arrival to the department, the specimens were subjected for adequate fixation using 10% formalin. After adequate fixation examination of the specimen for gross details according to the protocol for the examination of specimens of patients with carcinoma of breast was done with special emphasis to the size, multifocality and lymph node sampling. The representative tissue bits were subjected for routinely processing and paraffin embedding. Three-to-four-micron thick sections were taken from paraffin embedded blocks. These sections were routinely stained with H&E and were examined noting the findings as per proforma.

Tumors were typed according to the WHO classification system. The Nottingham modification of Bloom Richardson grading system was used for grading (Table 1). Grade 1 carcinoma includes tumors with combined scores of 3, 4 or 5; grade 2 includes scores of 6 and 7; and grade 3 includes tumors with the scores of 8 and 9. Each case was assessed considering important prognostic parameters like size of the tumor, histological grade, presence of necrosis, lymphovascular invasion and metastases in the axillary lymph nodes.

Table 1: Histological grading using Nottingham modification of Scarff Bloom Richardson system

Criteria	Score 1	Score 2	Score 3
Tubule formation	>75%	10-75%	<10%
Nuclear pleomorphism	Minimal variation in size and shape of nuclei	Moderate variation in size and shape of nuclei	Marked variation in size and shape of nuclei
Mitotic count/10HPF diameter	0-5	6-10	>11

All these cases were subjected to immunohistochemistry study for estrogen receptor (ER) and progesterone receptor (PR) from the representative areas of the tumor.

Inclusion criteria:

All the mastectomy and lumpectomy specimens of breast carcinoma submitted to the Department of Pathology irrespective of age were included in the study.

Exclusion criteria:

1. Lumpectomy specimens showing benign conditions, inflammation, and others.
2. Inadequate sample, extensive haemorrhagic and necrotic material.
3. Only the slides of carcinoma breast received for opinion.

Procedure of immunohistochemical staining:

Sections were cut at 3-4micrometer, mounted on to poly L lysine coated slides, and kept in incubator overnight at 65^0C. Sections were then deparaffinised and dehydrated using xylene and absolute alcohol for 30 minutes and 4 minutes respectively, followed by peroxidase block. Antigen retrieval was achieved by heat retrieval using antigen retrieval machine, containing Tris-EDTA buffer, pH 9, at temperature of 98^0C for 10minutes, 2 cycles. After allowing it to cool for 10-15 minutes, sections were washed with phosphate buffer. Then the sections were incubated with primary antibody, mouse monoclonal anti-ER and anti-PR antibody clone, for 30 minutes at room temperature. Subsequently the sections were washed with phosphate buffer and incubated with polymer horseradish peroxidase (HRP) secondary antibody (detection system) for 30minutes. Finally, the sections were washed and 3, 3-diaminobenzidine tetrahydrochloride (DAB) was used as chromogen to produce the characteristic brown stain and the sections were counterstained with haematoxylin. Each test was carried out with known positive control. Internal control was used wherever possible.

Assessment of immunohistochemical staining was done by using Allred scoring system (Table 2) by taking into consideration the proportion of stained cells (PS) and the intensity of staining (IS). A total score of 0-2 considered as negative and a score of 3-8 was considered as positive.

Table 2: Allred scoring system:

Proportion score (PS)	Positive cells (%)	Intensity score (IS)	Intensity of positivity
0	0	0	None
1	<1	1	Weak
2	1-10	2	Intermediate
3	11-33	3	Strong
4	34-66		
5	>67		

RESULTS:

The study was done in department of pathology, Al-Ameen Medical College, Vijayapur which comprises of "hormonal receptor status (ER & PR) in breast carcinoma" correlation with clinicopathological and prognostic parameters. The study was done for period of 3 years (June 2013- May 2016). During this period, total number of breast tumors was 316, of which 208 were benign lesions and 108 were malignant. The total number of cases included in the study was 108. The data was collected and analyzed as follows:

History:

In the present study, age of the patients ranged from 28-75 years. Mean age was 48 years. Majority of the patients (33.3%) were in the age group of 50-59 years, followed by 28.7% of patients belonged to age group of 40-49 years. All the patients were females and majority of the patients were premenopausal (60%). All cases (100%) were presented with lump in the breast, 105 cases (97.2%) with history of pain in addition to lump and 14 cases (13%) with ulceration of skin over breast in addition to lump in breast. None of the cases were presented with positive family history and past history of breast lesion**.** All the patients were multiparous women and had breast fed.

Physical examination: 31 cases (28.7%) had lump in left breast and 77 cases (71.3%) had lump in right breast. No bilateral breast involvement has been found in the present study. 66 cases (61.1%) were showing lump in upper outer quadrant and 23 cases (21.3%) in upper inner quadrant. Followed by, 8.3%, 4.6%, 2.8%, and 1.9% in lower outer, central, diffuse and lower inner quadrants respectively. 59 cases (54.6%) were having tumor size ranging from 2-5cms, followed by 48 cases (44.4%) with tumor size of >5cms and only 1(0.9%) case having < 2cms. 72 cases (66.7%) had lump which were fixed to breast, 21 cases (19.4%) were fixed to skin and in 15 cases (13.9%) lump was mobile. consistency of lump was hard in 89 cases (82.4%) and firm in 19 cases (17.6%). There were no soft consistency lumps found. 60 cases (55.5%) were presented with palpable axillary lymph nodes and in 48 cases (44.4%) axillary lymph nodes were not palpable.

Gross examination of the specimens: All the specimens in the present study were mastectomy specimens which included simple and modified mastectomy specimens. The gross examination findings of the specimens were as follows.

Size of specimens ranged from 13x10x4 cms to 18x12x5 cms. Axillary lymph nodes were present in only 60 cases. Size of lump was ranged from 2 to 11 cms, considering the largest dimension of the tumor. In the present study, majority of the cases had single tumor focus (93.5%), 5 cases (4.6%) had two tumor foci and only 2 cases (1.9%) had multiple tumor foci. Majority of the cases (55.6%) had infiltrating margins, followed by 41.7% of cases having well defined margins and 2.8% showing pushing margin. only 14 cases (12.9%) were showing nipple retraction, 21 cases (19.4%) had skin ulceration over the breast and 60 cases (55.6%) were showing lymph nodes on gross examination and dissection. Number of lymph nodes dissected was ranging from 1-10.

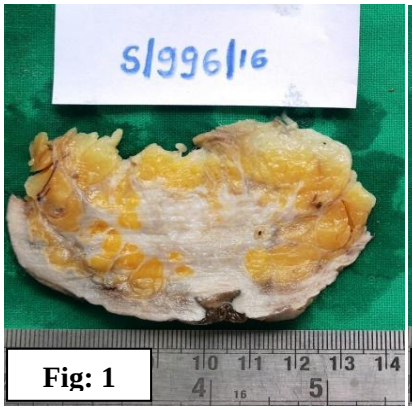


Fig: 1

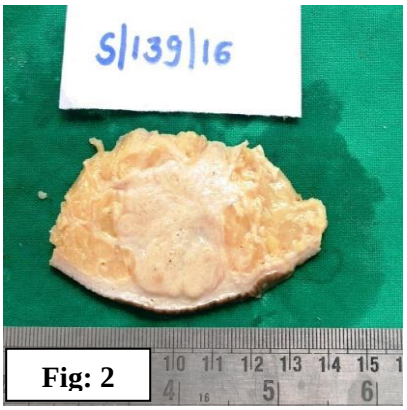


Fig: 2

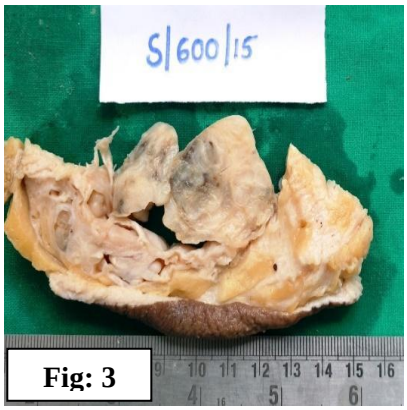


Fig: 3

Gross morphology of infiltrating ductal carcinoma showing greyish white tumor with infiltrating margins (Fig 1), medullary carcinoma showing greyish white tumor with pushing margins (Fig 2), invasive lobular carcinoma showing greyish white lobular tumor with ill-defined margins with cystic change (Fig 3).

Microscopic examination:

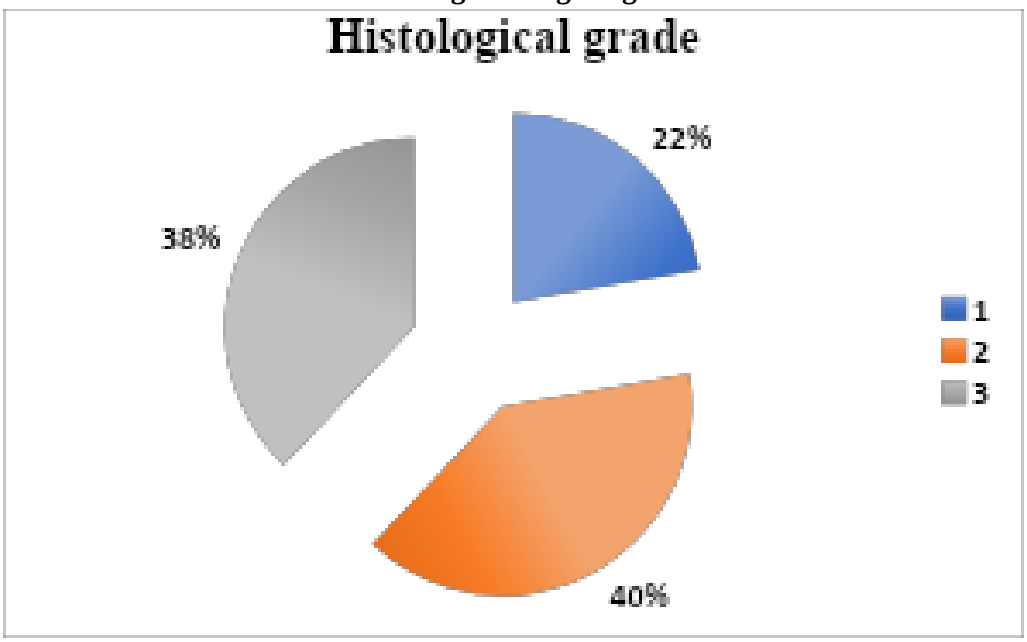
In this study, majority of the cases (85 cases, 78.7%) were of infiltrating ductal carcinoma, not otherwise classified, followed by 12 cases (11%) were of medullary carcinoma, 7 cases (6.5%) were of lobular carcinoma and 4 cases (3.7%) were of ductal carcinoma in-situ. (Table 3)

Table 3: Table showing different histological types of breast carcinoma

Histological type	No. of cases	%
Ductal carcinoma In-situ	4	3.7
Infiltrating ductal carcinoma	85	78.7
Lobular carcinoma	7	6.5
Medullary carcinoma	12	11.1
Total	108	100

Histological grade: 54 cases (50%) shows tubule formation in <10% of the tumor, followed by 49 cases (45.4%) shows tubule formation in 10-75% of tumor and only 5 cases (4.6%) shows >75% of tubule formation in the tumor. 54 cases (50%) showed marked pleomorphism of the nuclei in the tumor; followed by 44 cases (40.7%) showed moderate pleomorphism and 10 cases (9.3%) showed minimal pleomorphism of nuclei. 56 cases (51.9%) had mitotic count of 6-10/10hpf. Mitotic count of >11/10hpf was seen in 27 cases (25%) and 25 cases (23.1%) had mitotic count of 0-5/10hpf. With above features, 43 cases (39.8%) were of grade 2, followed by 41 cases (38%) were of grade 3 and 24 cases (22.2%) were of grade 1.

Chart 1: Chart showing histological grade of the tumor



Ancillary studies: 70 (64.8%) cases were ER positive and 61 (56.5%) cases were PR positive among 108 cases.

Table 4: Table showing ER status

ER status	No. of cases	%
Positive	70	64.8
Negative	38	35.2
Total	108	100

Table 5: Table showing PR status

PR status	No. of cases	%
Positive	61	56.5
Negative	47	43.5
Total	108	100

Table 6: Table showing ER and PR status

ER & PR	No. of cases	%
ER+ & PR +	58	53.7
ER+ & PR -	12	11.1
ER- & PR +	3	2.8
ER- & PR -	35	32.4
Total	108	100

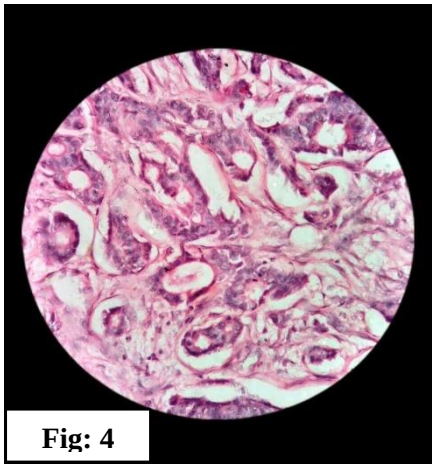
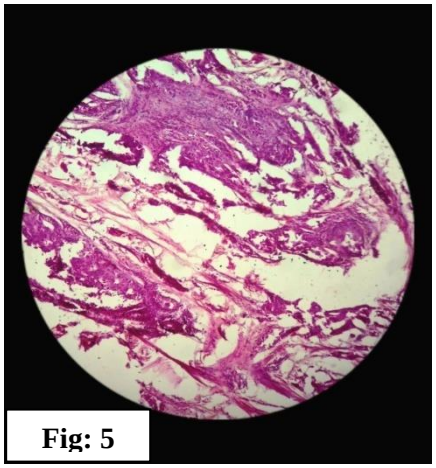


Fig: 4



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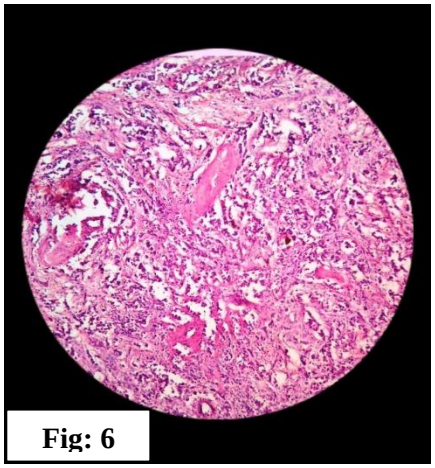

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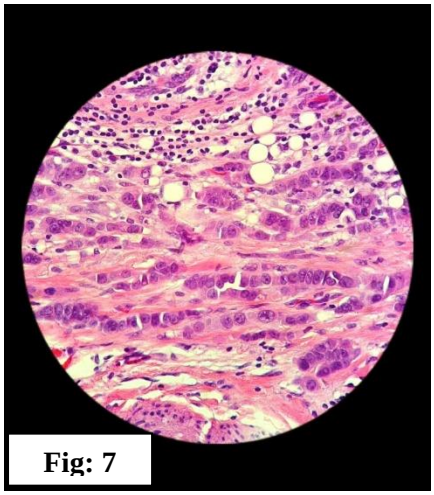


Fig: 7

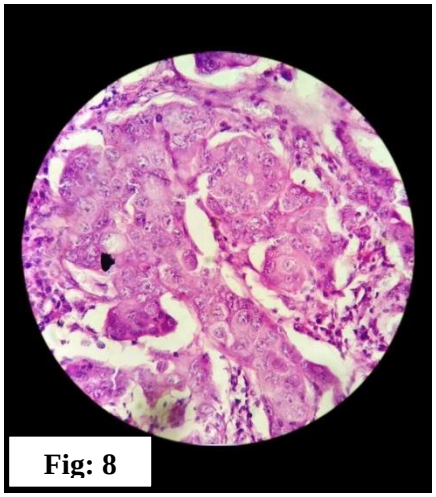


Fig: 8

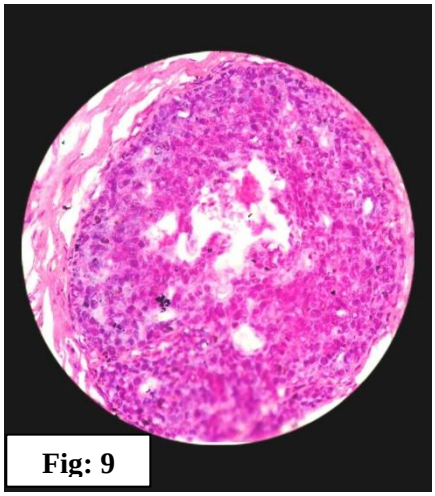
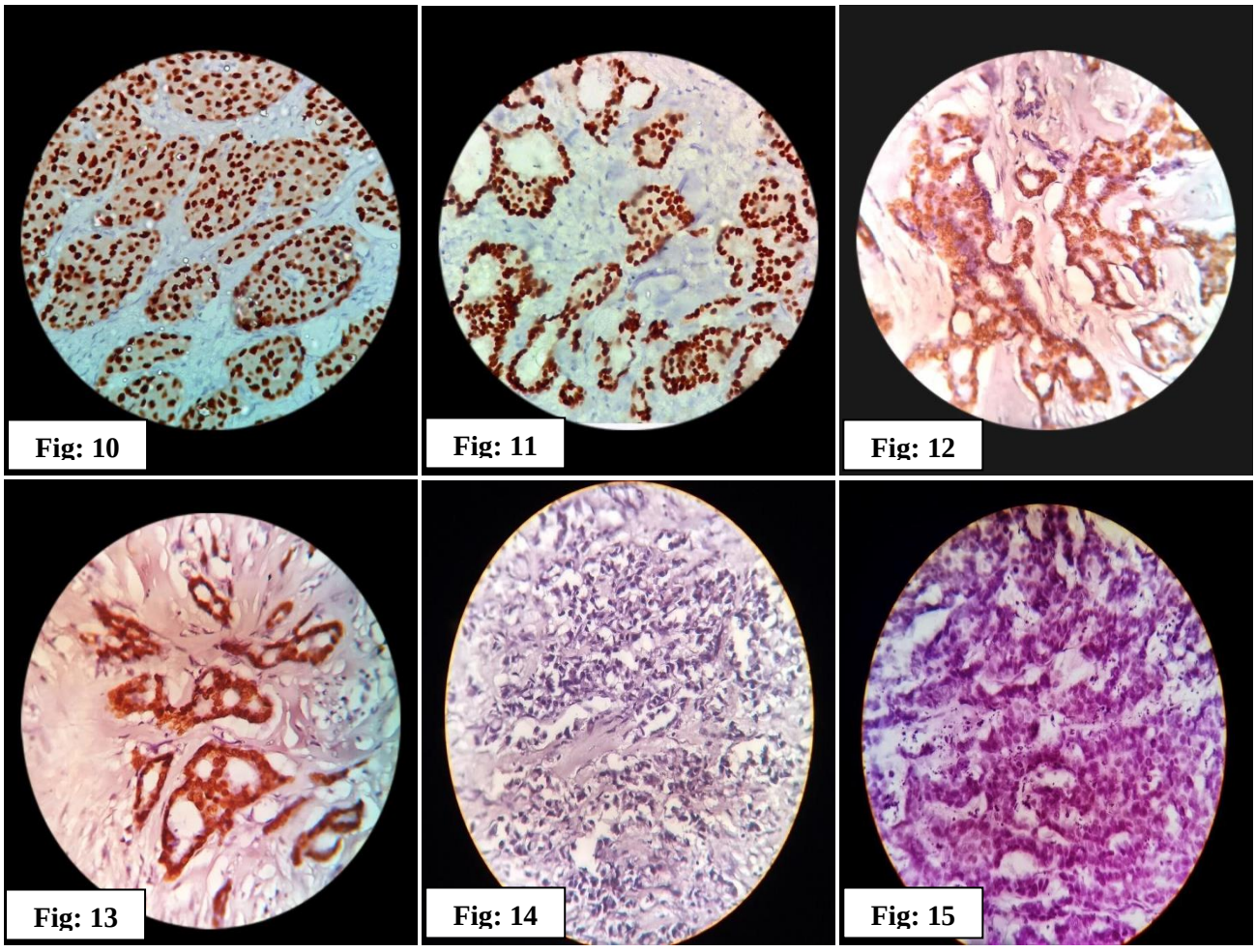


Fig: 9

Figures 4a: H & E (10X & 40X): Grade 1 infiltrating ductal carcinoma showing tubule formation by tumor cells, tumor cells showing mild pleomorphism with hyperchromatic nuclei and irregular nuclear margin. Grade 2 infiltrating ductal carcinoma showing focal tubule formation by tumor cells, tumor cells are showing moderate pleomorphism, sheets of tumor cells separated by fibrous tissue (fig 5). Grade 3 infiltrating ductal carcinoma showing absence of tubule formation, tumor cells showing marked pleomorphism, hyperchromatic and coarse chromatin (fig 6). Invasive lobular carcinoma showing tumor cells arranged in "Indian file" pattern, having hyperchromatic nuclei and prominent nucleoli. Background showing lymphocytic infiltration (fig 7). Medullary carcinoma showing syncytium-like arrangement of large tumor cells with marked pleomorphic nuclei, prominent nucleoli and frequent mitotic figures. Marked lymphocytic infiltration surrounding and within the tumor (fig 8). Ductal carcinoma in-situ showing tumor cells with pleomorphism, high grade nuclei and central necrosis. No invasion into the stroma seen. (fig 9)



ER(Fig 10) & PR (Fig 11) positivity in grade 1 infiltrating ductal carcinoma, ER (Fig 12)& PR(Fig 13)positivity in grade 2 infiltrating ductal carcinoma, ER (Fig 14) & PR(fig 15) negativity in grade 3 infiltrating ductal carcinoma.

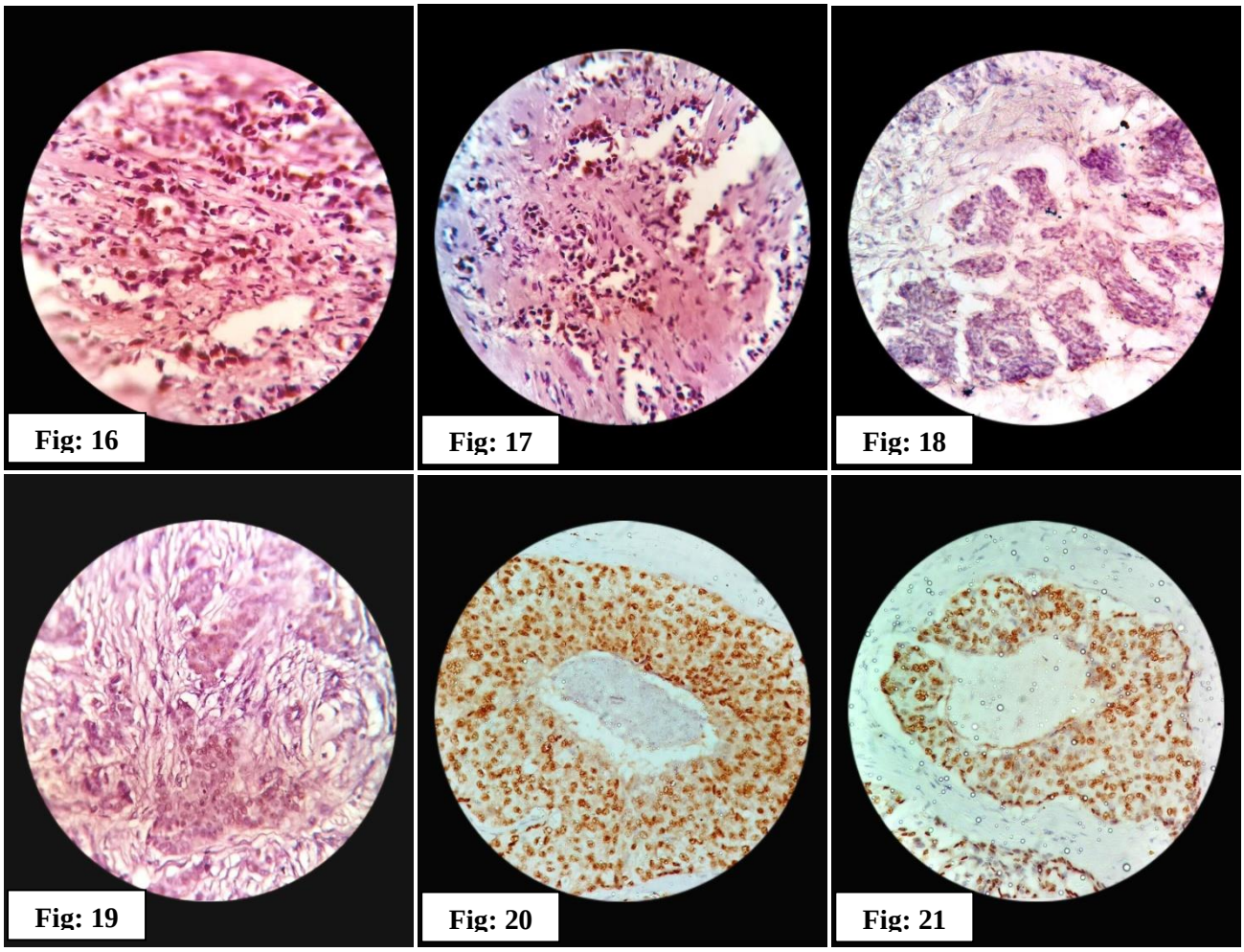


Fig: 16 Fig: 17 Fig: 18

Fig: 19 Fig: 20 Fig: 21

ER(Fig 16) & PR (Fig 17) positivity in lobular carcinoma, ER (Fig 18) & PR (Fig 19)negativity in medullary carcinoma, ER(Fig 20) & PR(Fig 21) positivity in ductal carcinoma in-situ

Correlation of each clinicopathological and prognostic parameters with ER and PR status:

Age: In the present study, majority of ER positivity cases (23 cases, 33.3%) were in the age group of 50-59 years. Even though, the incidence of breast carcinoma was more in this age group, ER expression (64.5%) has been slightly reduced in comparison with other age groups. Younger age group of 20-29 years shows 100% ER positivity, whereas, 30-39, 40-49, 60-69 and 70-79 years of age group were showing 66.7%, 64.5%, 62.5% and 50% of ER positivity. On applying hypothesis correlation test, there was negative correlation between age of the patient and ER status, as it was not statistically significant (P-value: 0.836).

Majority of PR positive cases (20 cases, 32.7%) were in the age group of 50-59 years. Expression of PR is highest in age group of 20-29 years (100%), followed by 30-39 (61.1%), 60-69 (56.3%), 40-49 (51.6%) and 70-79 (50%). On applying hypothesis correlation test, there was negative correlation between age of the patient and PR status, as it was not statistically significant (P-value: 0.723).

Tumor size: In this study, highest number of cases (59) was having tumor size ranging from 2-5 cms, among which 49 cases (83.1%) were showing ER positivity. Out of 48 cases, 40 cases (41.7%) were showing positivity for ER. Only 1 case was encountered having tumor size <2 cms, which is ER positive (100%). On applying hypothesis correlation test, there was positive correlation between size of the tumor and ER status, as it was statistically significant (P-value: <0.001). Maximum number of cases (59) was showing tumor size of 2-5 cms, among which 43 cases (72.9%) were PR positive. Out of 48 cases only 17 cases (35.4%) were PR

positive which belongs to tumor size >5 cms, followed by only 1 case (100%) was having <2 cms tumor size, which also had shown PR positivity. On applying hypothesis correlation test, there was positive correlation between size of the tumor and PR status, as it was statistically significant (P-value: 0.001).

Histological grade: Highest number of cases (43) were of grade 2 tumors, of which 36 cases (83.7%) were showing ER positivity. All the grade 1 tumors were showing ER positivity (24 cases, 100%). Out of 41 cases, only 10 cases (24.4%) were ER positive which belongs to grade 3. Expression of ER decreased as the grade of the tumor increased. On applying hypothesis correlation test, there was positive correlation between histological grade of tumor and ER status, as it was statistically significant (P-value: < 0.001). Out of 43 cases, 35 cases (81.4%) were showing PR positivity which belongs to grade 2, followed by, only 8 cases (19.5%) out of 33cases were showing PR positivity. Grade 1 tumors were showing maximum expression of PR (18 cases, 75%). On applying hypothesis correlation test, there was positive correlation between histological grade of tumor and PR status, as it was statistically significant (P-value: < 0.001).

Table 7: Table showing association of histological grade of the tumor with ER status

Grade	ER+		ER-		Total	p value
	N	%	N	%	N	
1	24	100.0	0	0.0	24	<0.001*
2	36	83.7	7	16.3	43	
3	10	24.4	31	75.6	41	
Total	70	64.8	38	35.2	108	

Note: *means significant at 5% level of significance (p<0.05)

Table 8: Table showing association of PR status with histologic grade of tumor

Grade	PR+		PR-		Total	p value
	N	%	N	%	N	
1	18	75.0	6	25.0	24	<0.001*
2	35	81.4	8	18.6	43	
3	8	19.5	33	80.5	41	
Total	61	56.5	47	43.5	108	

Note: *means significant at 5% level of significance (p<0.05)

Other prognostic parameters:

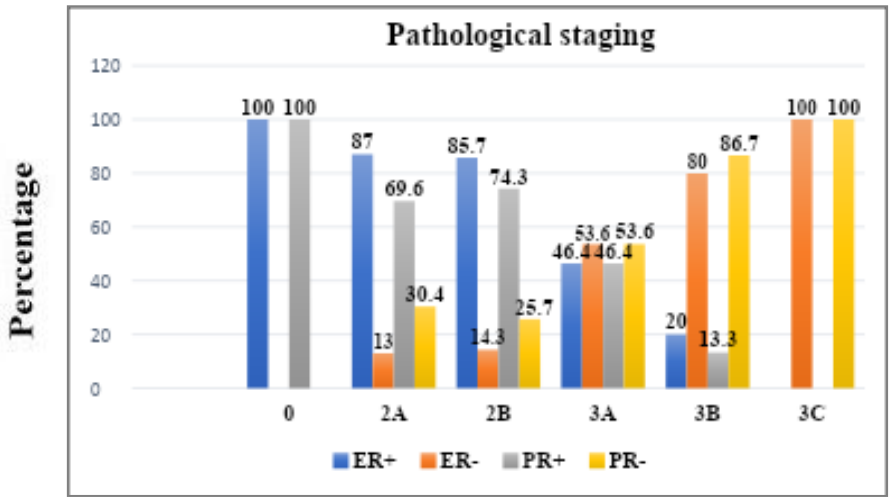
The expression of ER and PR was more in the tumors showing tubule formation in 10-75% of tumor, moderate nuclear pleomorphism and mitotic count of 6-10/10hpf. On applying hypothesis test, there was positive correlation between ER and PR status with histologic grade, nuclear pleomorphism and mitotic count, as the P-value is statistically significant. only 13 cases were showing lymphovascular invasion, among which only 3 (23.1%) of cases showing positivity for both ER and PR. There was a positive correlation between lymphovascular invasion and ER, PR status as P-value was statistically significant. 57cases were showing lymphnode involvement, of which 27 (47.4%) cases showing ER positivity. There was positive correlation between ER status and lymphnode involvement, as p-value (<0.001) was statistically significant. 57 cases were showing lymphnode involvement, of which 25 (43.9%) cases were showing PR positivity. There was positive correlation between PR status and lymphnode involvement, as the p-value (0.007) was statistically significant, the number of ER positive cases among those with 1-3 lymph node metastases was 53.8% which was higher than the 33.3% among those with more than 3 lymph node metastases. The number of PR positive cases among those with 1-3 lymph node metastases was 51.3% which was higher than the 27.8% among those

with more than 3 lymph node metastases. There was positive correlation between ER, PR status and lymph node involvement, as the P-value (0.001 & 0.005) was statistically significant. 9 (45%) cases out of 20 cases were showing ER positivity with necrosis. Only 8 (40%) cases were positive for PR with tumor necrosis. There was negative correlation between ER and PR status with necrosis, as P-value was not statistically significant (P-value- 0.134, 0.067).

Pathological stage:

In our study, majority of the cases which were of 2B pathological stage were ER (30 cases, 85.7%) and PR (26 cases, 74.3%) positive, followed by 2A stage showed ER (20 cases, 87%) and PR (16 cases, 69.6%) positivity. Expression of ER and PR were higher in low grade tumors, than in high grade tumors. There was a positive correlation between pathological grading and ER, PR status of the tumor (P-value: <0.001).

Graph 1: Graph showing association of ER and PR status with pathological staging



DISCUSSION:

Breast cancer comprises a heterogeneous group of tumors with a wide spectrum of morphologically and molecularly different subtypes, resulting in different biological behaviours, presentation, and prognosis. The major issue in making treatment decisions is to identify the subgroup of patients who will particularly benefit from a given treatment. A prognostic factor is any parameter available at the time of diagnosis that correlates with disease free or overall survival. Thus, it is indicative of the inherent biological aggressiveness of a tumor and is correlated with the natural history of the disease. A predictive factor indicates the likelihood of a response to a given therapy.[15] Breast cancer survival is linked to early detection, timely appropriate treatment and genetic predisposition.[16]

Consensus regarding the definitive prognostic/predictive analysis has yet to be reached, but significant progress continues to be made in the on-going search for a specific, rigorous and reproducible method of identifying successful treatment algorithms utilizing biological markers.[17]

In recent years several investigators demonstrated correlations between the presence of the hormonal receptor and various histopathological factors of primary breast carcinomas. These reports, however, yielded contradictory results. In several studies correlations between ER status and some histologic tumor types, like medullary, mucoid, or invasive lobular carcinomas, have been demonstrated. In some studies a relationship between histologic tumor grade and ER status was reported. In other investigations into these factors no such relationships could be demonstrated.[18]

The discrepancies may be the result of different methods of biochemical ER assay. Other reasons for the discrepancies may also be differences in evaluation and terminology, and variations of histopathological features within a tumor.[19]

Therefore, this study was performed to find whether correlations between ER and PR status, determined by immunohistochemistry, and histopathological features could be further clarified.

In our study, total of 108 cases of breast carcinomas were subjected to ER and PR status by immunohistochemistry using Allred scoring system. Maximum of ER (71.42%) and PR (66.6%) positivity was seen in patients of </=39years. Least positivity of ER and PR (50%) were seen in patients of age group >/=70years. There was negative correlation between age of patient and ER, PR status in the present study.

In Koonmee S et al[11] study, it was found that ER (72.73%) and PR (63.64%) positivity is highest in the age group of >/= 70years. The authors found that 50-59 years age group showed highest ER negative (58.33%) and PR negative (68.06%) cases.

Rana S et al[20] did similar study in the year 2016, showed maximum ER positivity (100%) in age group of 65-74 years and PR positivity in 75-84 years, followed by ER and PR positivity (80%) in age the group of 25-34 years. Considering all these discrepant observations, one may conclude that, age of the patient is not a specific parameter for determining ER and PR expression in the tumor.

In our study, 85 cases (78.7%) were of infiltrating ductal carcinoma, not otherwise specified type, in which 69.4% of cases were ER positive and 61.2% were of PR positive. There were 7 cases (6.5%) were of lobular carcinoma, in which all were ER positive and 71.4% cases were PR positive. Twelve cases of medullary carcinoma were encountered and all were negative for ER and PR. Ductal carcinoma in-situ cases were all positive for ER and PR. There was statistically significant correlation between histological type and ER, PR status.

In Stierer M et al[21] and Helin HJ[22] et al studies, similar changes were observed. Majority of the cases of infiltrating ductal carcinoma, not otherwise specified and lobular carcinoma were showing positivity for ER and PR. All the cases of medullary carcinoma type were negative for ER and PR. None of the above mentioned studies have considered ductal carcinoma in-situ in their study.

In this study, only 1 case of tumor size <2 cms was encountered, which was positivity of ER and PR both. Tumors of size 2-5 cms showed, 83% positivity for ER and 72.9% positivity for PR. There was significant correlation between size of tumor and ER, PR status.

In Dayal A et al[1] and Almasri NM et al[23] study, maximum ER positivity was shown by tumors of size <2 cms and maximum PR positivity was shown by tumors of size 2-5 cms. Least positivity for ER and PR was observed in tumors of size >5 cms. The authors also found no significant correlation between tumor size and ER, PR status. Azizun-Nisa et al[24] study showed a significant correlation between the size of tumor and ER, PR status. Maximum positivity for ER and PR was observed in tumors of size <2 cms

In our study, highest percentage of ER and PR positivity was seen in pathological stage 2 of tumor, followed by stage 3. There were no cases found with stage 1 and 4. There was significant correlation between pathological stage and ER, PR status in the present study. A similar study was done by Vedashree MK et al[25], who found maximum ER and PR expression was seen in stage 1 than stage 2 and 3. The authors found that, no significant correlation between the two parameters.

In the present study, grade 1 tumors showed highest ER positivity than grade 2 and 3, whereas, grade 2 tumors has shown more positivity for PR than grade 1 and 3. There was significant correlation between ER, PR status and histological grade of the tumor.

In Pathak B et al[14], Stierer M et al[21], Helin HJ et al[22], Koonmee S et al[11] , Dayal A et al[1], Narmadha R et al[26] (2017) and Kumar PK et al[27] (2014) studies, similar observations were made out. Maximum of ER and PR positivity were seen in grade 1 tumors, followed by grade 2 and grade 3 tumors. All the above mentioned studies showed significant correlation between histological grade and ER, PR status.

In our study, the expression of both ER was highest in the tumors showing tubule formation in <10% of tumor, and PR in 10-75% of tumors. Highest ER and PR expression was observed in tumors having mild nuclear pleomorphism and mitotic count of 0-5/10HPF. There was significant correlation between tubule formation and ER, PR status. In Stierer M et al[21] and Helin HJ et al[22] study, histological parameters of tumor differentiation were closely correlated with ER and PR status in that better differentiation was accompanied by higher prevalence of detectable ER. Similar observations were made by Berger et al[28] and Reiner et al[19] studies.

In the present study, 47.4% and 43.9% of axillary lymph nodes were showing ER and PR positivity respectively. Even though, there was less expression of ER & PR in the metastasized axillary lymph node, it was found that, there was positive correlation between them. Similar changes were observed in the studies of Dayal A et al[1] and Helin HJ et al[22].

In this study, the fraction of ER positive cases among those with upto 3 lymph node metastases was 53.8%, which was higher than the 33.3% seen among those with more than 3 lymph node metastases. The fraction of PR positive cases among those with upto 3 lymph nodes was 51.3%, which was higher than the 27.8% seen among those with >3 lymph node metastases. There was significant correlation between ER, PR status and number of lymph node metastases in the present study.

In Almasri NM et al[23] study, there was no significant correlation between number of lymph nodes showing metastases and ER, PR expression. Similar observations were made by Helin HJ et al[22] study and the authors found no significant correlation between axillary lymph node metastases and expression of ER and PR. Azizun-Nisa et al[24] study found significant correlation between number of lymph nodes involved and expression of ER and PR. The authors found expression of ER in group of lymph nodes (1-3 & >3) was more than expression of PR.

In the present study, grade 1(100%, 66.6%) and 2(100%, 100%) tumors were showing highest ER and PR expression. Necrosis was seen in high grade tumors more frequently than low grade. The better differentiated tumors had less necrosis and were more likely to express ER and PR. But this difference was not statistically significant in the present study. Similar observations were made by Helin HJ et al[22] study which showed significant inverse relationship between necrosis, tumor differentiation and ER, PR status.

CONCLUSION:

Carcinoma of the breast is the most common malignant tumor and the most common cause of death from carcinoma in females all over the world. A crucial development in evaluation of breast carcinoma has been the realization that the presence of ER & PR in the tumor tissue correlates well with response to hormone and chemotherapy. Immunohistochemistry (IHC) has an important role in the assessment of prognostic and predictive factors in breast carcinoma now-a-days. IHC is the most commonly used method of assessing hormonal receptor status, although other methods like FISH, biomarkers, etc., play a role in ER, PR testing.

The hormone receptors play a role in the development and progression of breast carcinoma and identify patients with lower risk of relapse and better overall survival. The determination of ER & PR on biopsies of breast carcinomas prior to therapeutic manipulations has become a standard practice in the management of breast carcinoma because it provides information on response to hormonal therapy and prognosis. In recent years, interest in prognostic factors has been stimulated by the success of systemic adjuvant therapy for early stage of breast carcinoma. A single parameter with strongest prognostic significance than other prognostic parameters is hormone receptor status.

So, present study is to see the correlation between hormonal receptors (ER & PR) and other prognostic parameters. High grade tumors are more likely to be ER, PR negative and such patients are not likely to respond to hormonal therapy as compared to patients with low grade tumors.

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