Original Research Article

"A STUDY ON EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CARCINOMA: A TERTIARY CARE HOSPITAL EXPERIENCE"

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ABSTRACT:

Background: Breast cancer is common cancer in women in both the developed and the less developed nations. Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer is now the most common cancer in most cities in India, and second most common in the rural areas. AIM: To evaluate the percentage of breast carcinomas expressing estrogen receptors and progesterone receptors and to correlate the ER & PR status with other prognostic parameters like histological type, grade, tumour size, and lymph node metastasis. Material & Methods: Study Design: Hospital based Prospective observational study. Study area: Dept. of. Pathology, in a tertiary care teaching college and hospital. Study Period: 1 year. Study population: patients who were resected for surgical breast specimens by modified radical mastectomy, lumpectomy or specimens and sent for pathological analysis. Sample size: study consisted a total of 100 patients. Sampling method: Simple Random sampling method. Inclusion Criteria: Carcinomatous lesions of breast. Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study. Study tools and Data collection procedure: The specimens were thoroughly grossed according to the standard protocol and those which fulfilled the inclusion criteria were evaluated for following data (1) tumour size (2) infiltration of the tumour to nipple and areola (3) infiltration onto posterior margin (4) necrosis (5) desmoplasia (6) calcifications and (7) number of lymph nodes involved. Statistical Analysis: The data was collected, compiled and compared statistically by frequency distribution and percentage proportion. Quantitative data variables were expressed by using Descriptive statistics (Mean \pm SD). Qualitative data variables were expressed by using frequency and Percentage (%). Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Chi-square test has been used.

Results:Out of 100 cases, of breast carcinomas most common phenotype is ER + & PR + 46 cases (46 %), followed by ER - & PR - which are 37 cases (37 %), followed by ER + & PR - 10 cases (10%), and ER - & PR + 7 cases (7%).

CONCLUSION: Immunohistochemically assessment of ER and PR status should be incorporated as a routine investigation. This along with histo-pathological grading will guide the clinicians to make correct choice of treatment protocols and help in improved quality of life for the patients.

Key words: Breast cancer, ER and PR status, breast specimens

INTRODUCTION:

Breast cancer is common cancer in women in both the developed and the less developed nations. Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer is now the most common cancer in most cities in India, and second most common in the rural areas. In India, around 0.15 million women were newly detected with breast cancer and nearly 70 thousand women died of breast cancer in 2012 ⁽¹⁾.

Traditional prognostic factors for breast carcinoma include the tumour size, axillary lymph node status, metastasis, the nuclear grade and histologic grade. The recently developed tumour receptor status evaluation helps to estimate a patient's response to endocrine therapy and their prognosis for clinical outcomes ⁽²⁾.

The importance of the receptor status is further emphasized by the introduction of newer molecular classification of breast carcinoma in St. Gallen International Expert Consensus ⁽³⁾. Although many markers have been evaluated, it is well known that Estrogen Receptor (ER) & Progesterone Receptor (PR) expressions are most useful in predicting response to therapy.

Most of the studies have shown positive association between the presence of positive estrogen and progesterone expression in the tumour cells with favorable prognosis ⁽⁴⁾. Evaluation of hormone receptor expression has become a central component of the pathological evaluation of breast cancer. The American Society of Clinical Oncology and the College of American Pathologists recommend testing for both ER and PR on all newly diagnosed cases of invasive breast cancer ⁽⁵⁾.

Breast cancer patients of Indian origin tend to be younger, with extensive tumour spread when first diagnosed and a large proportion had high-grade tumours and hormone-receptor negative tumours compared to Western series ⁽⁶⁾. The response rate is variable among different study groups. The hormone receptor expression in India was found to be low ⁽⁷⁾.

So the present study was undertaken to study the expression of estrogen receptor (ER) and progesterone receptor (PR) in breast carcinoma and to compare it with other prognostic parameters such as histological type, grade, tumour size, and patient's age.

AIM:To evaluate the percentage of breast carcinomas expressing estrogen receptors and progesterone receptors and to correlate the ER & PR status with other prognostic parameters like histological type, grade, tumour size, and lymph node metastasis.

Material & Methods:

Study Design: Hospital based Prospective observational study.

Study area: Dept. of. Pathology, in a tertiary care teaching college and hospital.

Study Period: 1 year.

Study population: patients who were resected for surgical breast specimens by modified radical mastectomy, lumpectomy or specimens and sent for pathological analysis.

Sample size: study consisted a total of 100 patients.

Sampling method: Simple Random sampling method.

Inclusion Criteria: Carcinomatous lesions of breast.

Exclusion Criteria:

- 1. Inflammatory conditions of breast (mastitis)
- 2. Non Neoplastic cysts of breast.
- 3. Benign epithelial lesions.

Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure:

The specimens were thoroughly grossed according to the standard protocol and those who fulfilled the inclusion criteria were evaluated for following data (1) tumour size (2) infiltration of the tumour to nipple and areola (3) infiltration onto posterior margin (4) necrosis (5) desmoplasia (6) calcifications and (7) number of lymph nodes involved.

After grossing tissue bits were subjected for routine processing, fixation, dehydration, clearing and embedding in paraffin wax. Sections were prepared from the blocks for routine staining Hematoxylin & Eosin (H&E).

During fixation, precautions were followed as hormone receptor study can be effected by the type of fixative used and also by over fixation or under fixation in formalin. Delayed fixation and heat fixation such as that by cautery also results in the degradation of receptor proteins.

The histopathological sections of breast carcinoma were reported according to WHO classification of breast carcinomas and graded by Modified Bloom Richardson's grading system. Those which fulfilled the inclusion criteria, t of those sections he paraffin blocks were subjected to ER & PR receptor study.

The specimens were processed by the HRP– polymer method. Protein retrieval was done by microwave technique and following antibody cloneswere used.

- 1. Mouse Anti-Human Estrogen Receptor alpha Clone 1D5.
- 2. Mouse Anti-Human Progesterone Receptor clone PgR636.

STAINING OF ER, PR WERE QUANTIFIED USING ALLRED SCORE

Allred scoring system was introduced in various university hospitals in North America to minimize the borderline cases and to put them into either positive or negative groups.

The Proportional score (PS) is as follows (8):

Score	% of Positive cells
0	0%
1	<1%
2	1 - 10%
3	11 - 33%
4	34 - 66%
5	67 - 100%

Intensity score (IS) is as follows (40):

0 - Negative

1 - Weak staining

2 - Intermediate staining

3 - Strong staining

Total score (TS): sum of Proportional score+ Intensity score;

0 - 2: Negative

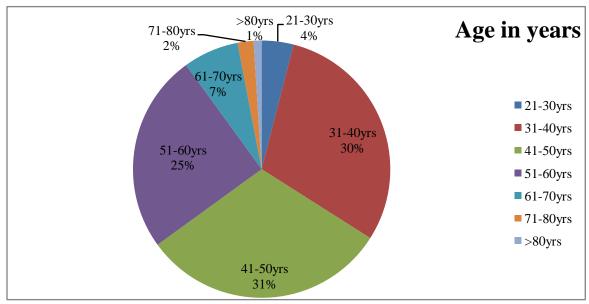
2 - 8: Positive

Total score greater than 2 is considered positive for significant expression of ER and PR. **Statistical Analysis:**

The data was collected, compiled and compared statistically by frequency distribution and percentage proportion. Quantitative data variables were expressed by using Descriptive statistics (Mean ± SD). Qualitative data variables were expressed by using frequency and Percentage (%). Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Chi-square test has been used to find the significance of study parameters on categorical scale between two or more groups. P values of <0.05 were considered statistically significant. Data analysis was performed by using SPSS Version 20.

OBSERVATIONS AND RESULTS:

Figure 1: AGE DISTRIBUTION IN THE STUDY POPULATION



In our study of 100 cases, age ranged from 28-82 years. Majority of the cases, 31 cases (31%) of them belonged to 41-50 years followed by 30 cases (30%) which belonged to the age group 31-40 years. Mean age for 100 cases is 47.66. The mean age for 41-50 is 46.25 and for 31-40 years are 36.36.

Table 1: Histological (MBR) grading in the study population

Histological grade	stological grade Number of patients %	
Grade I	41	41%
Grade II	47	47%
Grade III	12	12%
Total	100	100%

Out of 100 breast carcinoma cases which were graded according to Modified Bloom Richardson's grading system- majority 47 cases (47%) belong to grade II, 41cases (41 %) were in grade I and the remaining 12 cases (12 %) in grade III.

Table 2: number of cases positive for estrogen receptor

	ER	%
Negative	44	44%
Positive	56	56%
Total	100	100%

In our study, out of 100 cases it was observed that 56 cases (56 %) showed over expression of estrogen receptor so showed positive expression of the receptor while, in 44 cases (44%) there was no expression hence considered as negative or no expression of the receptor.

Table 3: number of cases expressing progesterone receptor

	Progesterone receptor	%
Negative	47	47%
Positive	53	53%
Total	100	100%

In our study of 100 cases, we observed that 53 cases (53%) showed expression of progesterone receptor hence are considered as positive for progesterone receptor, while 47 cases (47%) did not express the receptor hence considered as hormone receptor negative.

Table 4: showing expression of various phenotypes of ER & PR

phenotype	Number of patients	%
ER + / PR +	46	46%
ER - / PR -	37	37%
ER + / PR -	10	10%

ER- / PR +	7	7%
Total	100	100%

Out of 100 cases, of breast carcinomas most common phenotype is ER + & PR + 46 cases (46 %), followed by ER - & PR - which are 37 cases (37 %), followed by ER + & PR - 10 cases (10%), and ER - & PR + 7 cases (7%).

Table 5: showing correlation of variables with that of expression of ER

Variable	ER st	ER status		
	Negative(n=44)	Positive(n= 56)		
Tubule formation : >75%	3(6.82%)	10(17.85%)		
10 – 75%	20(45.45%)	28(50%)	0.139	
<10%	21(47.73%)	18(32.15%)		
Nuclear pleomorphism				
Minimal variation in size and shape of nuclei	8(18.18%)	20(35.71%)		
Moderate variation in size and shape of nuclei	22(50%)	30(53.57%)	0.016*	
Severe variation in size and shape of nuclei	14(31.82%)	6(10.72%)		
Mitosis				
0-5	13(29.55%)	31(55.35%)		
6 – 10	29(65.90%)	24(42.86%)	0.033*	
>11	2(4.55%)	1(1.79%)		
MBR grading				
I	11(25%)	30(53.57%)		
II	24(54.54%)	23(41.07%)	0.005*	
III	9(20.46%)	3(5.36%)	_	

Histologic variability			
Necrosis (n=27)	14(51.85%)	13(48.15%)	0.336
Pagetoid spread(n=3)	2(66.66%)	1(33.34%)	0.422
Lymphatic invasion(n=18)	12(66.66%)	6(33.34%)	0.032*
Vascular invasion(n=20)	14(70%)	6(30%)	0.009*

In view of statistical correlation with p value, Histological grading and nuclear pleomorphism, mitosis, lymphatic invasion and vascular invasion was found to be statistically moderately correlated with estrogen receptor positivity with p value.

Table 6: showing correlation of histological variables according to PR expression

Variables	PR status		P value
	Negative (n=47)	Positive(n=53)	
Tubule formation >75%	4(8.52%)	9(16.98%)	
10 – 75%	19(40.42%)	29(54.72%)	0.057
<10%	24(51.06%)	15(28.30%)	-
Nuclear pleomorphism			
Minimal variation in size and shape of nuclei	10(21.28%)	18(33.98%)	
Moderate variation in size and shape of nuclei	21(44.68%)	31(58.49%)	0.004*
Severe variation in size and shape of nuclei	16(34.04%)	4(7.55%)	
Mitosis			
0 - 5	13(27.66%)	31(58.49%)	
6 - 10	31(65.96%)	22(41.51%)	0.003*
>11	3(6.38%)	0	-
MBR grading			
I	12(25.53%)	29(54.73%)	

II	24(51.06%)	23(43.39%)	
III	11(23.40%)	1(1.88%)	0.001**
Histological variables			
Necrosis (n=27)	15(55.56%)	12(44.44%)	0.297
Pagetoid spread (n=3)	2(66.67%)	1(33.33%)	0.488
Lymphatic spread (n = 18)	13(72.22%)	5(27.78%)	0.180
Vascular invasion(n = 20)	15(75%)	5(25%)	0.005*

In view of statistical correlation with p value, Histological grading was strongly significantly associated with p value. Nuclear pleomorphism, mitosis, vascular invasion was found to be statistically moderately correlated with progesterone receptor positivity and p value.

Table 7: Showing expression ER and PR phenotypes in correlation with variables.

Variables	ER & PR status			P value
	ER+ PR+ (n=46)	ER- PR – (n=37)	ER+PR- &ER-PR +	
Tubule formation >75%	9 (19.56%)	3(8.11%)	(n=17) 1(5.88%)	0.173
10 – 75%	24 (52.17%)	15(40.54%)	9(52.94%)	1
<10%	13(28.27%)	19(51.35%)	7(41.18%)	-
Nuclear pleomorphism				
Minimal variation in size and shape of nuclei	17 (36.96%)	7(18.92%)	4(23.53%)	0.011*
Moderate variation in size and shape of nuclei	25(54.35%)	16(43.24%)	11(64.71%)	1
Severe variation in size and shape of nuclei	4(8.69%)	14(37.84%)	2(11.76%)	
Mitosis				
0 - 5	28(60.87%)	10(27.02%)	6(35.29%)	0.021*
6 - 10	18(39.13%)	25(67.57%)	10(58.82%)	1
>11	0	2(5.41%)	1(5.89%)	

MBR grading				
I	27(58.69%)	9(24.32%)	5(29.42%)	0.003*
II	18(39.14%)	19(51.35%)	10(58.82%)	
III	1(2.17%)	9(24.33%)	2(11.76%)	
Histological variables				
Necrosis (n=27)	10(37.03%)	12(44.44%)	5(18.53%)	0.535
Pagetoid spread (n=3)	1(33.34%)	0	2(66.67%)	0.504
Lymphatic spread (n =18)	4(22.23%)	11(61.11%)	3(16.66%)	0.046*
Vascular invasion (n = 20)	4(20%)	13(65%)	3(15%)	0.011*

In view of statistical correlation with p value, Histological grading was strongly significantly associated with p value.

Nuclear pleomorphism, mitosis, vascular and lymphatic invasion was found to be statistically moderately correlated with progesterone receptor positivity and p value. Tubule formation was better with ER+ PR+ phenotype than compared to ER- PR- . Tubule formation of $<\!10\%$ was seen more in ER – PR- than in ER+ PR+. Tubule formation if $>\!75\%$ was seen more in ER+ PR+ group. However there was no significant correlation. Higher nuclear pleomorphism with sever pleomorphism was seen in ER- PR- group when compared to ER+ PR+ and showed statistically significant correlation. Mitosis of score $>\!11$ was seen more in ER- & PR- and also in ER+ PR - & ER- PR + group with no case in ER+ PR +. Mitotic score of 0-5 was seen more in ER+ PR + than in ER – PR - .

In the present study histological grading in correlation with ER/PR positivity was found to statistically significant correlation was observed. The majority of the cases are grouped in the phenotype ER+ & PR+, with 27 cases (58.69%) in grade I, 18(39.13%) in grade II, 1(2.17%) in grade III. Among ER- & PR- group 19 cases (51.35%) in grade II, and 9 cases (24.32%) belonged to grade I and grade III. In the present study among grade I tumors, 27 cases (58.69%) were ER+ & PR+ and only 9 cases (24.32%) were ER- PR-. Among grade III tumors, only 1 case was ER+ & PR+, while 9 cases (24.32%) were ER- &PR-. Grade II had majority of the cases out of which18 cases (39.13%) were ER+ & PR+ &19 cases (51.35%) were ER-PR-.

Vascular invasion was seen more common among ER- & PR – group than ER+ PR+ group and also showed significant correlation. Lymphatic invasion was seen more in ER- PR- group than ER+ PR+ group; however there was no significant correlation. Necrosis was seen more in ER- PR - group than in ER+ & PR+ group but it was not statistically significant.

Pagetoid involvement was seen more in ER- PR+ and ER+ PR - group than in ER+ PR+, however there was no significant correlation.

DISCUSSION:

Breast cancer accounts for 19-34% of all cancer cases among Indian women. As per the data from national and regional cancer registries, it is the commonest cancer and is listed as the second leading cancer among women in India. Early breast carcinoma constitutes only 30% of the breast cancer cases seen at regional cancer centers in India, whereas it constitutes 60-70% of cases in the developed world.

A project was conducted by WHO called GLOBOCON ⁽¹⁾, to compare the incidence of breast cancer in India, with that of western countries like USA and China for the year 2012. According to the research done by WHO, it was found out that US, India and China account for almost one third of the global breast cancer burden. The following were the observations of the project for the year 2012.

	India	USA	China
Number of newly	1,44,937	2,32,714	1,87,213
detected cases			
Mortality	70,218	43,909	47,984

According to the observations of the project GLOBOCON, India has the highest mortality of women dying due to breast cancer, when compared to USA and China. Persistent efforts over last 40 to 50 years in the USA and China have resulted in a large proportion of women presenting in early stages and therefore there has been a consistent decrease in the death rates due to breast cancer.

Though the incidence of breast cancer in India was less when compared to USA and China there is significant increase in mortality, due to many reasons like lack of awareness, screening programme, social stigma, etc hence present at comparatively late stages and do not survive even after treatment. WHO predicts for the year 2015 in India thatthere will be an estimated 1, 55,000 new cases of breast cancer and about 76000 women in India are expected to die of the disease. GLOBOCON 2012 ⁽¹⁾, in relation with NATIONAL CANCER REGISTRY AND IARC international agency for research on cancer a specialized branch of WHO.

"Spectrumof Breast cancer in Asian women "by Gaurav Agarwal ⁽¹⁷⁾ & S.Y. Cheung et al, multi-national collaborative study which compared the demographic, clinical, pathological and outcomes data in breast cancer patients at breast cancer centers in India, Malaysia and Hong Kong. Data showed that the incidence of breast cancer is lower, yet the cause-specific mortality is significantly higher in developing Asian countries compared with developed countries in Asia and the rest of the world.

The following data that has been represented here has been referenced from the following official Indian registries, which are subsets of the

National Cancer Registry Programme:

- Three Year Report of the Population Based Cancer Registries 2009 2011.
- Consolidated Report of the Hospital Based Cancer Registries 2007 2011.

According to PBCR (Public Based Cancer Registeries) which was set up in various places like Chennai, Mumbai & Bengaluru the following data was collected. The overall incidence of breast carcinomas with respect to other cancers and its prevalence among the age groups of the present years was compared with that of statistics obtained for the year 1982 -1983.

State	Incidence		Age group <=50yrs	
	1982 - 1983	2009 -2011	1982-1983 2009 -2011	
Mumbai	20% of all cancers	30% of all cancers	30 - 35% 52%	
Chennai	20% of all cancers	27% of all cancers	30 –35 % 49%	
Bangalore	15% of all cancers	27% of all cancers	30-35% 53.2 %	

This table shows the trend of increased incidence in breast carcinoma cases over the past few decades. It also shows the clear shift of the most common age group to < 50 years. In the present study out of 100 cases most of the cases who presented with breast carcinoma were under <= 50 years were 65 cases, while cases with >50 years were 35 cases.

In the present study minimum age that presented with breast carcinoma was 28 years, the maximum age which presented with breast carcinoma was 82 years and the most prevalent age group involved in the present study was 41-50 years followed by 31-40 years.

The mean age of involvement is 47.73. The present study was compared with that of other studies, Lobna Ayadi et al $^{(10)}$, Shushan Shweta et al $^{(11)}$ & Urmila et al $^{(12)}$. In all these studies the majority of the patients who presented with breast carcinoma were <50 years and it correlated with the findings of the present study. In Shushan et al $^{(11)}$, the age group involved are 23-70 years with mean age 54.4 and in Urmila et al $^{(12)}$ the age group involved is 23-80 years with mean age is 51.5.

In India, the average age of developing a breast cancer has undergone a significant shift over last few decades. 25 years back, out of every 100 breast cancer patients, 2% were in 20 to 30 years age group, 7% were in 30 to 40 and 69% of the patients were above 50 years of age.

Presently, 4% are in 20 to 30 yrs age group, 16% are in 30 to 40, 28% are in 40 - 50 age group. So, almost 48% patients are below 50 years age group. An increasing numbers of patients are in the 25 to 40 years of age, and this definitely is a very disturbing trend. A women's reproductive history is highly associated with risk of breast cancer. The disease occurs more frequently among women who have an early menarche, who are nulliparous and late age of menopause.

In the present study, histological grading was done according to modified Bloom Richardson's grading, majority of the cases, 47 cases (47%) were diagnosed as grade II of MBR staging, followed by 41 cases (41%) as grade I and 12 cases (12%) as grade III.

This study was compared with other studies, Zafrani et al ⁽¹³⁾, Le Doussal et al ⁽¹⁴⁾, Onitilo AA et al ⁽¹⁵⁾, Peiro G et al ⁽¹⁶⁾&Shushanshwetha et al ⁽¹¹⁾. In all these studies the breast carcinomas were graded by MBR grading system. In all these studies grade II cases were most common and findings were similar with that of my study. In the other studies grade III was found to be next common after grade II, but in the present study grade I cases were next most common after grade II.

In an another study conducted by Zubair Ahmad &Amnakhurshid et al⁽¹⁷⁾, based on significance of prognostic factors that included tumour grading, axillary lymph node status and modified Bloom Richardson's grading showed that out of 120 cases 5 (4.17%) were grade I, 91(75.83%) were grade II, and 24(20%) were grade III. Thus in his study also majority of the cases were grade II and are similar to that of the present study.

Out of 100 cases, breast carcinomas were subjected to IHC procedure, progesterone receptor expression was found to be positive in 53 cases (53%) and the expression of progesterone receptor was found to be negative in 47 cases (47%). The observations of the present study were compared with other studies like Zafrani et al (13) and Shushan Shweta et al (11). In these studies, Zafrani et al, out of 793 cases which were included in their study showed estrogen receptor positive in 81% of the cases& progesterone receptor expression was seen in 63% of the cases. In the study conducted by Shushan Shweta et al out of 75 cases, on which IHC procedure was done estrogen receptor expression was seen positive in 76% cases and progesterone receptor expression was seen in 58.7% of the cases. All these studies showed majority of the cases expressed in ER & PR receptor status.

In the present study, immunohistochemistry was done and they are grouped into the following phenotypes. In the present study out of 100 cases, most common phenotype obtained is ER + & PR + 46 cases (46%), followed by ER - & PR – phenotype are 37 cases (37%). The observations of the present study were compared with other studies R Kim et al $^{(18)}$, Dunwald KL et al $^{(19)}$, Nadji M et al $^{(20)}$. In R Kim et al $^{(18)}$, majority of the cases expressed the hormonal phenotype ER + & PR+ were 62.1 %, followed by ER - & PR – with 20.5%, ER + & PR – 12.3% & ER- & PR+ 20.5 %. The observation of R Kim et al was similar to that of the present study. Dunwald et al study showed majority of the cases were ER + & PR + 63%, followed by ER - & PR – 21

%, ER + & PR – were 13%, and ER - & PR + were 3%. The observation of Dunwald KL $^{(19)}$ et al were similar to that of the present study with majority of the cases were ER + & PR+.

In the present study histological grading in correlation with ER&PR positivity was found to be statistically significant. In the present study histological grading in correlation with ER positivity was found to be statistically significant (p<0.001). Among ER+ group 30 cases (53.6%) were grade I, 23 cases (41.07%) were grade II, 3 cases (5.35%) were grade III. Histological grading also showed correlation with the expression of PR positivity was found to be statistically significant (p<0.001). Among the expression of PR hormone receptor grade I were 29 (54.71%), grade II were 23 (43.4%), and grade III were 1 (1.88%). The observations of the study were compared with Hemalatha et al (21) and Pathak T &Bashyal et al (222).

CONCLUSION:

Immunohistochemically assessment of ER and PR status should be incorporated as a routine investigation. This along with histo-pathological grading will guide the clinicians to make correct choice of treatment protocols and help in improved quality of life for the patients.

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