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ROLE OF PROGESTERONE RECEPTOR STATUS AS AN INDEPENDENT PROGNOSTIC INDICATOR IN HORMONE RECEPTOR POSITIVE OPERABLE INVASIVE BREAST CANCER

Oncology

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ABSTRACT

Introduction: Hormone receptor expression in breast cancer carries a strong prognostic value and also predicts response to hormonal therapy in these patients. The value of progesterone receptor (PR) status independent of the estrogen receptor (ER) status has remained unproven with conflicting reports. This study aimed at identifying any independent prognostic value associated with PR expression in Luminal-A, or Luminal-B type operable invasive breast cancer.

Material and methods : Retrospective analysis of the prospectively maintained data was done for patients who presented to our institution with invasive breast cancer and underwent curative surgery between 2002-2006. All patients found to have ER positivity were included in the study. Data on PR expression pattern was assessed using multivariate analysis for prognosis with respect to disease free survival (DFS).

Results : Total 1256 patients underwent curative surgery for invasive breast cancer over a period of 5 years (2002- 2006). Of the total 854 patients included in the analysis, 596 had positivity for both ER and PR, isolated ER positivity was found in 246 patients, while only 12 patients were found to be PR positive in the absence of ER positivity. HER2 positivity was noted in 175 of these patients. A significant trend was seen towards improved outcomes in PR positive patients with respect to DFS at 10 years (*p* value-0.01). This survival benefit was maintained even in the presence of lymph node metastases, and in patients treated with or without chemotherapy. This benefit, however, was not seen in patients with high grade (modified Bloom Richardson grade 3) tumors (*p* value-0.4).

Conclusion: PR expression in hormone receptor positive operable IBC was found to be an important variable of prognosis, independent of the ER expression status. And, its presence was associated with an improved DFS in hormone receptor receptor positive operable IBC.

KEYWORDS:

Introduction

Breast cancer is well recognized as an estrogen dependent disease, and this fact has been used successfully for management of these patients. Hormone receptor positivity in breast cancer signifies good prognosis and is a predictor of response to various endocrine therapies available for these patients.

Progesterone receptor is a member of a large family of nuclear receptors, and is activated by the binding of progesterone as its ligand. Research has shown that the synthesis of progesterone receptor (PR) is positively regulated by the presence of estrogen receptor (ER) expression.[1,2] Expression of ER, with or without PR expression is seen in up to 80% cases of breast cancer, while an isolated PR positivity is a relatively uncommon phenomenon, reported variably within a range of 0.3%-7% cases.[3-6]

In a study reported in 2004, the need to move away from routine PR testing was emphasized upon, and it was based on the argument that PR expression did not add to any additional prognostic information, and did not lead to any change in the patient management.[7] This study, however, was in contradiction to some other studies.[4,8,9] Moreover, to add to this confusion, some of the national guidelines (NICE guidelines UK 2009) do not recommend for a routine evaluation for PR expression in the management of breast cancer patients.[10]

Thus, while the prognostic and predictive role of ER expression is well established in carcinoma breast, the independent prognostic value of PR expression remains controversial.

This study aimed to identify an independent prognostic and predictive role of PR expression in operable invasive breast cancer.

Material and methods

Study population

The study was designed as a retrospective analysis of the prospectively maintained data for the breast cancer patients treated at our institute. Data was collected for patients diagnosed with, and treated for operable invasive breast cancer between 2002-2006 at our institute, a tertiary cancer center. All these patients underwent curative surgery. Adjuvant therapy was given as per institutional protocols. Patients found to have a Luminal-A or Luminal-B subtypes on histopathological examination were included in the analysis. Institutional scientific review board clearance was taken for use and analysis of the data.

Pathology

Review of the histopathology was done by an experienced oncopathologist at our institute. Positivity for ER/PR expression was defined by using Allred score based upon the proportion of stained cells and intensity of staining on immunohistochemistry (IHC) examination using antibodies for ER (EP1 clone), and PR (Pgr-636 clone). A total Allred score of 3 or more was considered positive for receptor expression.[11] HER2-neu receptor testing was done in all cases, and receptor expression was defined based upon the 2013 ASCO/CAP guidelines. All specimens underwent HER2 testing with IHC study. An IHC score (2013 ASCO/CAP guidelines) of 0 or 1+ was considered a negative result, a score of 3+ was considered positive for HER2 expression. Those with an equivocal IHC score of 2+ underwent FISH testing, and those showing a HER2/CEP17 ratio of ≥2 were classified as having HER2 gene amplification, a ratio of <2 was considered was considered negative for HER2-neu.[12]

Follow up

After completion of therapy, all patients were followed-up at regular intervals according to the institutional practice. Each follow up visit included a thorough history and clinical examination, and investigations as dictated by the history or clinical examination. Annual mammography was done routinely for contralateral breast in all patients. All follow up data was obtained from the department of epidemiology and medical records in our institute.

Outcome analysis

Any suspected recurrence, either locoregional or distant, was evaluated clinically, with imaging, and also pathologically for confirmation, except in cases of bone metastases, where a positive bone scan finding was taken as proof of metastases without pathology. The primary endpoint was Disease-free survival (DFS), and was defined as the time-period extending from the date of surgery until identification of the first recurrence.

Statistical analysis

Statistical analysis was done using SPSS version 21.0 software. A Chi-square test with Yates' correction was used for analyzing the data for associations**.** Survival analysis was done using the Kaplan-Meier curves. Cox regression method was used for the multivariate analysis of the various subgroups.

Results

Patient characteristics

Total 1256 patients underwent curative surgery for invasive breast cancer at our institute from 2002 to 2006. The median age at diagnosis in the study population was 49 years (range 34-68 years), with 619 patients (73.58%) being >40 years of age. Of these, 854 (67.99%) cases were found to have hormone receptor positivity, and were included in the study. Surgical treatment given in these patients included modified radical mastectomy in 84.4% cases, and breast conservation surgery in 15.6% cases. Chemotherapy was given in 810 (96.3%) patients, based upon appropriate indications. Adjuvant trastuzumab was given in patients with tumor showing a positive HER2-neu expression. Adjuvant radiation therapy was given in 261 (30.99%) patients. All patients received adjuvant endocrine therapy for 5 years. Median follow up period in our study was 48 months (range 26-120 months).

Among the 854 cases, 596 patients had ER+/PR+ disease, 246 had ER+/PR-, while only 12 patients (1.4%) had ER-/PR+ disease. In view of the very small number of ER-/PR+ cases, i.e. only 1.4%, these patients had to be excluded from the survival analysis. Thus, the total number of patients included in the survival analysis was 842. Of these cases, HER2 positivity was seen in 175 patients (figure 1).

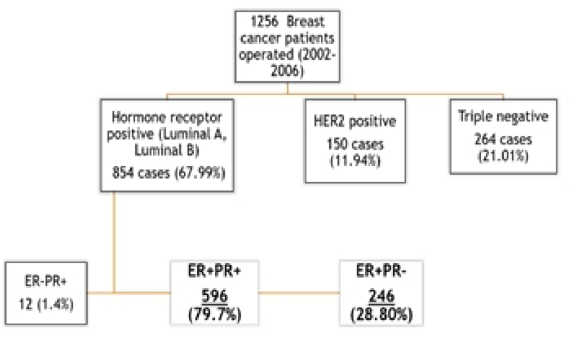


Figure 1. Study population (n=842).

Clinicopathologic characteristics

Tumor size as noted in the study population was ≤2 cm in 95 (11.28%) patients, >2 cm but ≤4 cm in 357 (42.4%), and >4 cm in 390 (46.32%) patients; 505 (59.86%) patients had node positive disease on final histopathology examination. Tumor grade distribution included grade-I in 111 (13.18%), grade-II in 383 (45.49%), and grade-III tumors in 348 (41.33%) patients. Similarly, presence of lymphovascular space invasion was seen in 302 (35.86%) cases (table 1).

Table 1- Clinicopathological features in the study groups

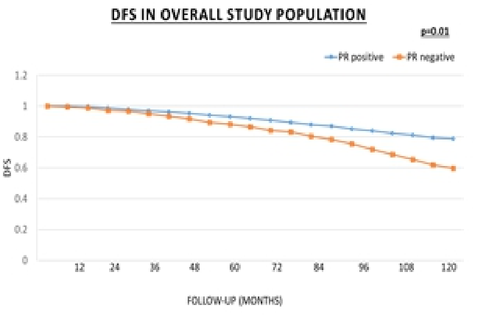
N=842	PR positive n=596 (70.78%)	PR negative n=246 (29.22%)	*p* value
Age			0.0001
≤40 (223)	108 (18.12%)	115 (46.75%)	
>40 (619)	488 (81.88%)	131 (53.25%)	
Tumor size			0.175
≤20 mm (95)	63 (10.57%)	32 (13.01%)	
20-50 mm (357)	245 (41.11%)	112 (45.53%)	
>50 mm (390)	288 (48.32%)	102 (41.46%)	
Nodal metastasis			0.31
Positive (505)	351 (58.89%)	154 (62.6%)	
Negative (337)	245 (41.11%)	92 (37.4%)	
Grade			0.0007
I (111)	81 (13.59%)	30 (12.19%)	
II (383)	293 (49.16%)	90 (36.59%)	
III (348)	222 (37.25%)	126 (51.22%)	
LVI			0.5
Yes (302)	218 (36.58%)	84 (34.15%)	
No (540)	378 (63.42%)	162 (65.85%)	
HER2 status			0.02
Positive (175)	112 (18.79%)	63 (25.61%)	
Negative (667)	484 (81.21%)	183 (74.39%)	
Surgery			0.76
MRM (710)	504 (84.56%)	206 (83.74%)	
BCS (132)	92 (15.44%)	40 (16.26%)	
Chemotherapy			0.05
Yes (810)	568 (95.30%)	242 (98.37%)	
No (31)	27 (4.7%)	4 (1.63%)	
Radiotherapy			0.9
Yes (261)	189 (31.7%)	72 (29.26%)	
No (581)	407 (68.3%)	175 (70.74%)	

Absence of PR receptor expression was found to be significantly associated with HER2-neu positivity (*p* value- 0.02), grade III tumors (*p* value- 0.0007), age at diagnosis ≤40 years (*p* value- 0.0001), and the need for adjuvant chemotherapy (*p* value- 0.05). There was, however, no significant association of PR receptor expression with tumor size, presence of nodal metastases, lymphovascular invasion, or type of surgery performed (table 1).

Survival analysis

The disease free survival (DFS) was calculated at 10 years for the study population in both the groups. There was statistically significant difference in the DFS between the PR-positive and the PR-negative groups, with the PR-positive group showing a better DFS of 78.8% versus 59.75% in the PR-negative group (*p* value- 0.01) at 10 years (figure 2).

Figure 2. DFS at 10 years in the study population. A significantly better DFS was seen in the PR positive group (*p* value 0.01)



On subgroup analysis, a significant difference in the DFS was maintained in the patients irrespective of the nodal status (*p* value- node positive 0.05, node negative 0.03) (figure 3), those with low-grade disease (*p* value- 0.04) (figure 4), and those who received chemotherapy (*p* value- 0.02) (figure 5). There was, however, no difference in the DFS between the PR-positive and the PR-negative groups in patients with high-grade disease (*p* value- 0.09) (table 2, figure 4).

Table-2 Disease-free survival in various subgroups (univariate analysis)

	Disease free survival (%)		
	PR positive	PR negative	p value
Chemotherapy group	78.66	59.78	0.02
No-chemotherapy group	74.19	50	NA
Node positive	80.34	69.75	0.05
Node negative	85.30	70.5	0.03
High grade (grade III)	63.9	54	0.09
Low grade (grade I, II)	87.96	75.3	0.04

Figure 3. DFS at 10 years based on nodal status showing significant difference in DFS between the PR+ and PR- groups in node positive, and node negative subgroup

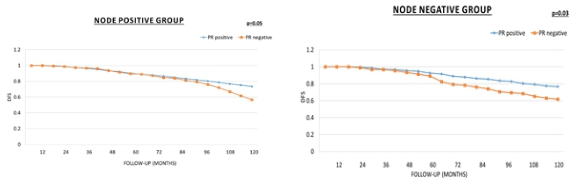


Figure 4. DFS in grade subgroups. Effect of PR status on DFS can be seen in the low-grade group (*p* value 0.04), while the high grade subgroup shows no significant difference between the two groups (*p* value 0.09).

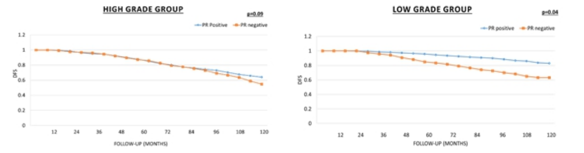
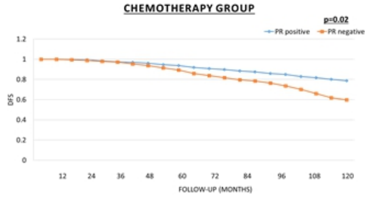


Figure 5. DFS in the patients receiving chemotherapy. Curve showing significant survival benefit in patients with PR+ disease (univariate analysis)



To negate the confounding effect of various factors over the DFS, multiple regression analysis was performed. In this analysis, the subgroups with node positive disease (HR 1.30, 95% CI 0.58-3.15, *p* value <0.001), node negative disease (HR 1.45, 95% CI 0.56-2.87, *p* value <0.001), and those with low grade disease (HR 1.30, 95% CI 0.56-3.20, *p* value 0.04) were found to still maintain the difference in DFS between the PR-positive and the PR-negative disease groups. The subgroup receiving chemotherapy and those with high grade disease, however, did not show any significant difference in DFS between the two groups (table 3). The confounding effect of radiation therapy on recurrence between the two groups was nullified by the almost equal proportion of patients who received radiotherapy in PR-positive and PR-negative groups, 31.7% and 29.26%, respectively.

Table-3 Multivariate survival analysis among various subgroups

Subgroup	Hazard ratio	95% CI	p value
Hormone therapy	1.36	0.58-3.15	<0.001
Nodal positivity	1.30	0.56-2.87	<0.001
Nodal negativity	1.45	0.62-3.10	<0.001
Chemotherapy group	1.21	0.45-3.22	0.55
High grade	1.16	0.32-1.98	0.07
Low grade	1.30	0.56-3.20	0.04

Discussion

Breast cancer is no longer considered a homogeneous disease entity, and the molecular subtypes of breast cancer not only define the prognosis in these patients, but also predict response to hormonal or anti-HER2 therapies. Accordingly, hormone receptor positivity in breast cancer is known to carry a better prognosis, and, this has widely been defined in terms of ER positivity only. An independent prognostic role of PR expression in breast cancer has remained controversial over time. Some authors have even questioned the need for a routine PR testing in breast cancer management.[7]

In our study, PR negativity was significantly associated with a younger age (≤40 years) at presentation, and high-grade disease. It probably represents the relatively aggressive biology of the PR negative disease, making it present at a younger age with high-grade tumors. A positive PR expression in our study was also found to be associated with ER expression (only 1.4% isolated PR positivity), and a negative HER2 expression. So, PR positivity was more likely in older women with low grade, ER positive, HER2 negative breast cancers, which, broadly, forms the good prognosis group of breast cancer patients. These findings are also supported by the previously reported studies by Liu et al, and Purdie et al.[5,13] No association was, however, found with the lymph node status, or the tumor size with the PR expression pattern.

An isolated PR positivity is a relatively uncommon occurrence, reported with a range from 0.3%-5% in literature, and, in the present study, it was seen in 1.4% patients. In view of the small number of patients in this subgroup, no meaningful observations could be made pertaining to the DFS in this subgroup. This small incidence has led some authors to refute a clinical advantage to the routine PR testing, putting its cost-effectiveness as the supporting argument.[7] In this subgroup of patients (ER-/PR+), studies have shown PR expression to predict response to tamoxifen in the premenopausal patients.[4,14] And further, the level of PR expression was found to be associated with the degree of response to tamoxifen in these patients.[14]

Even in patients with ER+ disease, PR expression has been shown to affect the response to tamoxifen. In the present study, all patients were treated with hormonal therapy, and the recurrence rate was significantly higher in patients with ER+/PR- disease as compared to ER+/PR+ disease. Similarly, Osborne et al[15] showed a higher response to tamoxifen in ER+/PR+ tumors as compared to ER+/PR- disease. In the study by Arpino et al, ER+/PR- tumors were more likely to show tamoxifen resistance and aberrant growth factor signalling when compared to ER+/PR+ tumors.[9] Also, in the Arimidex or Tamoxifen Alone or in Combination (ATAC) trial, there was significantly higher advantage of anastrozole over tamoxifen in the ER+/PR- tumors as compared to that in ER+/PR+ tumors, where only a modest advantage over tamoxifen was seen.[16] These data suggest that even in ER+ disease, PR expression pattern might act as a useful guide in the selection of appropriate hormonal therapy (tamoxifen followed by an aromatase inhibitor versus upfront aromatase inhibitor). As mentioned previously, presence of ER expression positively regulates the synthesis of PR, and thus PR positivity may indirectly indicate a higher functional status of ER protein, leading to a better response to tamoxifen in ER+/PR+ patients.[1,2] This phenomenon, however, to be used as a guide for therapy-selection, needs further testing in clinical trials.

Taking into account various subgroups in the present study, we notice that in the high-grade subgroup, the prognostic effect of PR expression is probably weakened by the biologically aggressive nature of high-grade disease, as notified by the absence of any significant difference in the DFS between the PR+ and PR- groups in this subgroup. Also, in patients who received chemotherapy, multivariate analysis did not show any difference in the DFS between the two groups. While in the study by Purdie et al, a significant difference in the DFS was noted between the two groups in those who received chemotherapy.[13] This could be due to the small number of patients in the present study, who did not receive chemotherapy (31 patients), thus making the analysis in this subgroup statistically irrelevant.

Equally important is the methodology used for the testing of PR expression. Previously, ligand binding based assays were used for testing ER and PR expression, and thus predicting the response to hormonal therapy in breast cancer.[17] Later, in mid 1990s, a switch over to IHC based assays was noted the world over because of the advantages of IHC, including low cost, and less time required to perform the test. Further, IHC methods were found to be superior to ligand binding assays for predicting outcomes in these patients.[18,19] Even with the IHC methodology, a lack of standardisation was noted in the reporting patterns. For example, in the BIG 1-98 study, initially the hormone receptor expression data provided from the local laboratories was used for analysis. Later on, review of the tumor sections at the central pathology office was done. The results showed a significant discordance between the results seen from local laboratories and the central pathology office. In this analysis, discordance was more pronounced for PR expression.[20] In our study, the receptor expression analysis was done by the oncopathologist using standardised probes, and methodology as per the 2013 ASCO/CAP guidelines, thus avoiding the risk of any false results.

Looking at the present study broadly, one can deduct that PR expression in breast cancer holds an important prognostic value. And, while in advanced cases where a need for adjuvant chemotherapy is defined by other high risk features, like tumor size, and nodal status, the pattern of PR expression may be particularly useful when deciding about the need for adjuvant chemotherapy in early breast cancer cases, when there are no other indications for chemotherapy. For example, ER+/PR- and node negative, low grade breast cancer may be considered for adjuvant chemotherapy in view of the higher recurrence risk imparted by PR negativity. Further, isolated PR expression may identify patients who might still benefit from hormonal therapy.

Conclusion

In the present study, PR positive tumors were associated to have a better DFS across various subgroups based on clinicopathological features. A higher response to hormonal therapy in the form of lower recurrence rate was found in the ER+/PR+ as compared to the ER+/PR- group.

However, the idea behind a routine PR testing goes beyond just the identification of the rare patients with an ER-/PR+ disease, and also extends to include identification of those patients with ER+/PR- tumors, who will show a relative resistance to the tamoxifen therapy, with an aggressive tumor biology. In fact, as mentioned previously a PR negative status in otherwise low risk disease can be used as an indicator of need for chemotherapy, especially in the resource limited settings where test like Oncotype-DX may not be easily available.

Standardisation of the testing methods and reporting protocols is equally important, and any deficiency on this part may cause false results, leading to inadequate management of the patients, as well as misinterpreted outcomes and varying survival analyses in relevant studies. Thus, to conclude, PR receptor not only forms an indispensable part of the breast cancer management, but also provides important prognostic and predictive information in these patients, independent to that provided by the ER expression alone, particularly in the early breast cancer patients.

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