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ORIGINAL ARTICLE

Progesterone receptor status in determining the prognosis of estrogen receptor positive/ HER2 negative breast carcinoma patients

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Summary

Purpose: *To evaluate the impact of progesterone receptor (PR) status on estrogen receptor (ER)-positive and HER2-negative breast cancer.*

Methods: *A total of 1673 operable breast cancer patients, diagnosed from June 1984 to June 2011 were retrospectively reviewed and 400 patients with ER-positive and HER2-negative tumors were identified and evaluated. ER-positive and HER2-negative patients were classified into two groups: group A: ER+/PR-/HER2- and group B : ER+/PR+/HER2- according to PR status.*

Results: *Median follow-up was 14.2 years (range 10.1-18.2). The ratio of postmenopausal patients was significantly higher in group A (68.2%, p=0.015). Grade 1 tumor and stage I disease were significantly higher in group B (15%, p=0.007 and 15%, p=0.005, respectively). Mean overall survival (OS) and disease free survival (DFS) were significantly better in group B (15.3±1.5 years vs 8.7±0.8 years, p=0.032; 10.5±1.6 years vs 5.7±0.5 years, p=0.022) as compared with group A. Relative risk for recurrence and death were two-fold higher in group A (p=0.05 and p=0.01, respectively).*

Conclusion: *PR status exerts a significant impact on prognosis of ER+/HER2- breast cancer.*

Key words: *breast cancer,estrogen receptor, HER2, progesterone receptor,prognosis*

Introduction

Breast cancer is no longer considered a unique disorder since Perou et al. described the molecular profiling of human breast tumors [1]. Subsequent published reports have contributed to better understanding the clinical behavior of breast cancer subtypes [2]. In routine daily practice, many medical oncologists decide for adjuvant treatment of their own patients with breast cancer based on the immunohistochemical staining of ER and HER2 along with tumor size and axillary lymph node status. Nearly 75% of breast cancers express ER and about half of them co-express PR at the same time [3]. Estrogen and ER are required for the synthesis of PR [4]. The pathogenesis of ER-positive and PR-negative tumors is still a matter of debate. Both ER and PR status provides information that predicts response to therapy. However, very few studies examined the PR content alone as a prognostic factor. At the present time, the crucial question is whether PR status has a significant impact on recurrence rate and survival of ER(+)/HER2(-) breast cancer. Whether PR status plays a role on recurrence rate and/or survival of ER(+)/HER2(-) breast cancers and if so, whether it should influence the decision of adjuvant therapy are not yet fully clarified. The question whether

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there is a marked difference between the characteristics of PR(+) and PR(-) breast cancers has not been answered yet.

This retrospective study principally aimed to determine a relationship between PR status and the prognosis of ER-positive and HER2-negative breast cancer. Also we intended to examine the diversity of clinicopathologic characteristics of PR status in breast tumor with immunohistochemically determined ER(+)/HER2(-).

Methods

Patients

The data of 1673 breast cancer patients, who underwent surgery and received therapy (neoadjuvant/adjuvant chemotherapy, hormonal therapy and radiotherapy) between June 1984 and June 2011, were retrospectively reviewed. Patient data were obtained from the hospital registration system. Patients whose data were not fully accessible and who had stage 4 disease at the time of diagnosis were excluded, thus a total number of 400 patients with ER(+)/HER2(-) tumors were included. ER(+)/HER2(-) patients were subclassified into two groups according to PR status. Group A included PR(-) cases [ER(+)/PR(-)/HER2(-)] and group B consisted of PR(+) cases [(ER(+)/PR(+)/HER2(-)]. ER and PR tumor status was determined by immunohistochemistry (IHC) and considered positive if at least 1% of cells were stained positive for ER and PR. HER2 status was assessed by measuring the number of HER2 gene copies using IHC. A tumor was classified as HER2(+) if it was scored as 3+. If IHC was scored 2+, then reflex testing using in situ hybridization (ISH) was performed on the same specimen. And if IHC was scored 1+ then it was considered as HER2(-).

Statistics

Descriptive values obtained from the data were presented as mean±SD, median (minimum-maximum), and number and frequency as percentages. The relationships between the structures of categorical characteristics of the groups were examined by chi-square test. Independent t-test samples were used to compare the numerical characteristics of the two groups.

DFS was calculated from the date of diagnosis until recurrence. OS was defined as the interval between the date of diagnosis and death from any reason or the date of the last follow up. Kaplan-Meier method with log rank test were used to compare OS and DFS. In addition, Cox regression model was used to determine the effective factors on OS and DFS. Statistically significance level was set at $p<0.05$ and the PASW (SPSS version 18) program was used.

Results

Clinical and pathological characteristics

Eighty-eight (22%) breast cancer patients were included in group A and 312 (78%) in group B. The median age of patients in group A and B were 57.5 (range 23-98) and 51 (range 21-80) years, respectively. The ratio of postmenopausal patients was significantly higher in group A when compared to that of patients in group B (68.2 vs 52.9%, p=0.015). The most common histopathological type was invasive ductal carcinoma in both groups. Histologically, grade I tumors were significantly more in group B (15 vs 6%, p=0.007). The ratio of grade 2 and 3 tumors was similar in both groups. Ki-67 values were available for 5 patients in group A and for 52 patients in group B . The mean Ki-67 values were similar between two groups (23±4.6 vs 31±3.1, p=0.1). Sixty-three percent of all of the patients had node-positive disease. The patients in group A had a significantly higher axillary lymph node positivity compared to those in group B (74 vs 60%, p=0.025). The number of patients with stage I disease was significantly higher in group B (15 vs 5%, p=0.005), but the number of patients with stage II and III disease were similar in both groups. There was no statistically significant difference between the groups in relation to tumor size, histological type and nodal stage (N1,N2,N3). Bone was the most common site of metastasis in both groups (50 vs 52%, p=0.6). Although there was no statistically significant difference between the two groups for the first site of recurrence, the recurrence rate was higher in group A (46%, N=40 vs 29%, N=91, p=0.005). Brain metastases occurred more frequently in group B (5%, N=15, p=0.03). The patient demographic and clinicopathological characteristics are shown in Table 1.

Treatment characteristics

All of the patients underwent surgery (mostly modified radical mastectomy, N=355, 88.7%). Treatment characteristics (adjuvant chemotherapy, neoadjuvant chemotherapy, hormonal therapy, radiotherapy) were similar between the two groups (p>0.05 for each one). Anthracycline-based chemotherapy was the predominant chemotherapy in both groups (51.9 and 51.4%). All of the patients were given hormonal therapy and tamoxifen was used more frequently than aromatase inhibitors (AIs) in both groups regardless of the menopausal status (56% in

Table 1. Patient demographic and clinicopathological characteristics

Characteristics	*Group A (PR-) N (%)*	*Group B (PR+) N (%)*	*p value*
Median, age, years (range)	57.5 (21-80)	51 (23-98)	
Menopause			
Post	60 (68)	165 (53)	0.015
Pre	28 (32)	147 (47)	
Tumor stage			
T1	11 (13.4)	57 (20.4)	
T2	49 (59.8)	155 (55.4)	0.440
T3	19 (23.2)	53 (18.9)	
T4	3 (3.7)	15 (5.4)	
Nodal stage			
N0	21 (25.9)	109 (40.1)	
N1	25 (41.7)	59 (36.2)	0.025
N2	11 (18.3)	42 (26.4)	
N3	24 (40)	61 (37.4)	
Grade			
G1	5 (5.7)	46 (14.7)	
G2	35 (40.2)	140 (44.9)	0.070
G3	19 (21.8)	72 (23.1)	
Unknown	28 (32.2)	54 (17.3)	
Histological type			
IDC	69 (80.2)	253 (81.6)	0.760
ILC	8 (9.3)	18 (5.8)	
Others	9 (10.5)	38 (12.2)	
Ki 67 (mean±SD)	5 (23±4.6)	52 (31±3.1)	0.120
TNM stage			
I	5 (6)	46 (14.8)	
II	39 (45)	132 (42.6)	0.050
III	43 (49)	132 (42.6)	
Recurrence			
Yes	40 (45.5)	91 (29.3)	0.050
No	48 (54.5)	220 (70.7)	

PR: progesterone receptor, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma

Table 2. Treatment characteristics of ER+/HER2(-) patients

Characteristics	*Group A (ER+) N (%)*	*Group B (PR-) N (%)*
Surgery		
MRM	80 (92)	299 (89)
BCS	5 (6)	33 (10.5)
Others	3 (2)	3 (0.9)
Adjuvant chemotherapy		
Yes	68 (77.3)	257 (82.4)
No	20 (22.7)	55 (17.6)
Neoadjuvant chemotherapy		
Yes	2 (2.2)	13 (4
No	86 (97.8)	299 (96)
Chemotherapy regimens		
Anthracycline-based	36 (51.4)	134 (51.9)
Taxane-based	32 (45.7)	110 (42.6)
CMF	2 (2.9)	14 (5.5)
Radiotherapy		
Yes	76 (86.4)	273 (87.5)
No	12 (13.6)	39 (12.5)
Hormonotherapy		
TAM	47 (56)	156 (51.5)
AI	23 (27.4)	78 (25.7)
Switch (TAM->AI)	11 (13.1)	48 (15.8)
Extended adjuvant	2 (2.4)	5 (1.7)
TAM + GNRH	1 (1.2)	16 (5.3)
Types of AI		
Letrozole	8 (29.6)	44 (46.8)
Anastrozole	13 (48.1)	36 (38.3)
Exemestane	6 (22.2)	14(14.9)

MRM: modified radical mastecomy, BCS: breast-conserving surgery, TAM: tamoxifen, CMF: cyclophosphamide,methotrexate,5-fluorouracil, GNRH: gonadotropin-releasing hormone, AI:aromatase inhibitor

group B, 57% in group A). Comparison of the AIs revealed that anastrozole was used more frequently in group A (48.1%) whereas letrozole was used more frequently in group B (46.8%) (Table 2).

Survival

Median follow-up was 14.2 years (range 10.1-18.2) for the whole cohort. Mean OS and DFS were significantly better in group B (15.3±1.5 years vs 8.7±0.8 years, p=0.032; 10.5±1.6 years vs 5.7±0.5 years, p=0.022) (Figures 1 and 2). Survival after the first recurrence was similar between the two groups (37.7±6.2 months vs 44.4±6.1 months, p=0.2) (Table 3, Figure 3).

Relative risk for recurrence and death were two-fold higher in group A compared with group B (p=0.05 and p=0.01, respectively) (Table 4).

Table 3. Mean survival according to groups

Survival	*Group A*	*Group B*	*p value*
Overall survival (years)	8.7 ± 0.8	15.3 ± 1.5	0.032
Disease free survival (years)	5.7 ± 0,5	10.5 ± 1.6	0.022
Survival after recurrence (months)	37.7 ± 6.2	44.4 ± 6.1	0.200

In group B, median DFS and OS of the patients treated with tamoxifen were significantly higher than that of the patients treated with AIs (10.7±0.7 and 11.1±1.4 years, p=0.05 and p=0.045, respectively). Risk of death in patients treated

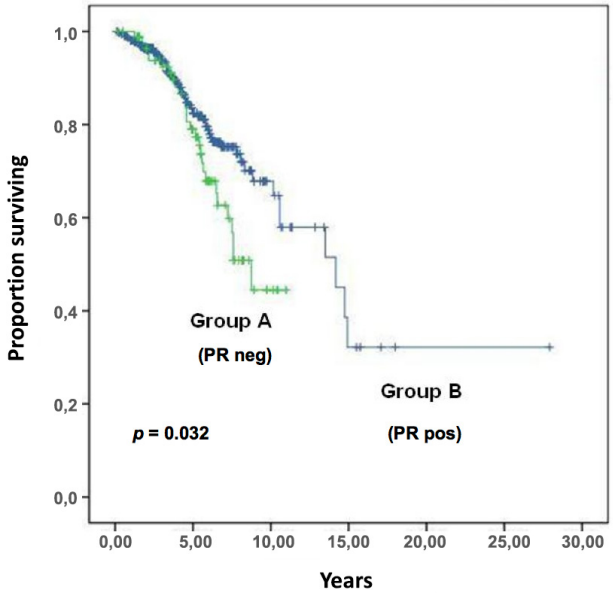

Figure 1. Overall survival for ER(+)HER2(-) breast carcinoma patients according to PR status.

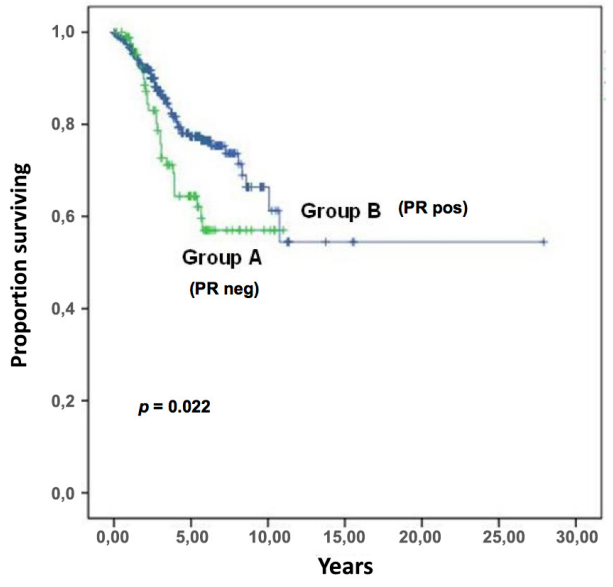

Figure 2. Disease free survival for ER(+)HER2(-) breast carcinoma patients according to PR status.

with AIs was more than 2.0-fold and 0.14-fold less in tamoxifen-AI switch therapy when compared to tamoxifen monotherapy in group B (p=0.045 and p=0.007, respectively). When the effects of hormonal therapy on OS and DFS were evaluated in group A, the risk of death was 0.13-fold lower with switch therapy and 0.134-fold lower with AI monotherapy when compared to tamoxifen monotherapy (p=0.0047 and p=0.05, respectively) (Table 5).

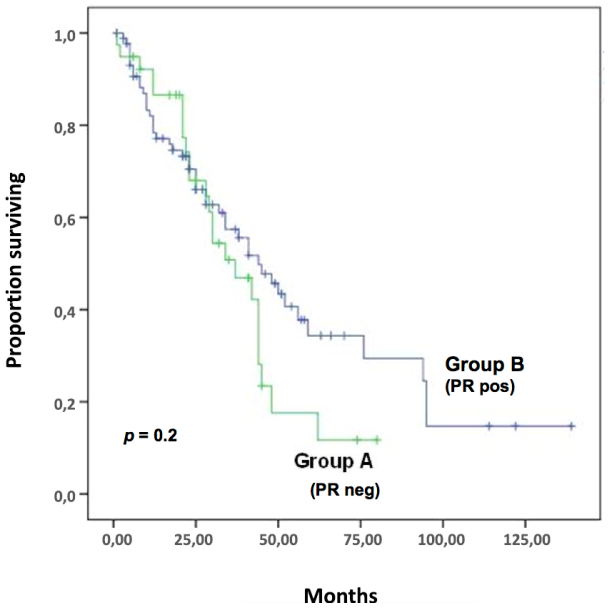

Figure 3. Overall survival after first recurrence of ER(+)/HER2(-) breast carcinoma patients according to PR status

Table 4. Relative risk for recurrence and death in group A compared to group B

	RR	*95% CI*	*p value*
Recurrence	2.015	1.24 - 3.27	0.005
Death	2.0	1.17 - 3.40	0.010

RR: relative risk, CI: confidence interval

Discussion

Estrogen and ER play an important role in breast cancer. Therefore, various therapies targeting this pathway are used in breast cancer patients in the adjuvant or metastatic setting. In the past, some of the ER (+) patients were found to be less responsive to hormonal treatment and PR status was suggested to guide the determination of response to hormonal therapy [4]. It was demonstrated that not only ER status but also PR status was a significant marker for predicting response to hormonal therapy [5,6].

In several studies it was found that ER (+) / PR (-) tumors have their own epidemiologic features [7,8]. ER (+) and PR (-) tumors are more common in elderly patients [8]. This may be particularly explained by the decreased estrogen levels in postmenopausal women, which supports the theory of insufficient PR expression due to low

Table 5. Logistic regression analysis of the two groups

	Group A				*Group B*			
	OS		*DFS*		*OS*		*DFS*	
	HR (95%CI)	*p value*	*HR (95%CI)*	*p value*	*HR (95%CI)*	*p value*	*HR (95%CI)*	*p value*
TAM	*Reference category*				*Reference category*			
AI	1.296 (0.558-3.01)	0.546	0.134 (0.018-1.018)	0.050	2.083 (1.016-4.271)	0.045	1.006 (0.506-1.998)	0.987
Switch (TAM->AI)	0.129 (0.017-0.970)	0.047	0.874 (0.380-2.012)	0.751	0.141 (0.034-0.586)	0.007	0.119 (0.029-0.493)	0.003
Extended adjuvant†	0.000 (0.0-)*	0.984	0.000 (0.0-)*	0.984	0.000 (0.0-)*	0.969	0.000 (0.0-)*	0.971
TAM +GNRH	0.000 (0.0-)*	0.990	0.000 (0.0-)*	0.989	0.325 (0.045-2.370)	0.268	0.279 (0.038-2.027)	0.207

* 95% CI upper limit not calculated in this category due to the low number of patients. †Refers to use of AI after 5 years of TAM or AI. HR:hazard ratio, TAM:tamoxifen, GNRH: gonadotropin-releasing hormone, AI: aromatase inhibitor, OS: overall survival, DFS: disease free survival

circulating levels of endogenous estrogen even if the ER pathway is active [9,10]. This result was supported in the current study.

In a retrospective study Arpino et al. reported that ER (+)/PR (-) tumors behaved more aggressively with higher proliferation rates, S-phase fraction, aneuploidy ratio, and had higher levels of HER1/HER2 [11]. In addition, some other studies suggested that there may be a relationship between decreased PR levels and high HER2 activity [12]. Phosphatase and tensin homolog (PTEN), which is a negative regulator of the HER family receptor pathway, may correlate with PR levels indirectly. Loss of PTEN activates HER pathway and subsequently seems to correlate with loss of PR [13]. Additionally, it was shown that loss of heterozygosity (LOH) in the region of 10q23 harboring PTEN was associated with specific loss of PR in 30-40% of breast cancer cases [14]. On the other hand, activation of the HER family receptor pathway not only down-regulates PR levels, but also activates abnormal ER signaling which may partly explain the resistance to tamoxifen of ER(+)/PR(-) tumors [15,16].

In our study the percentage of patients receiving tamoxifen and having postmenopausal status was higher in group A [ER(+)/PR(-)/HER2(-)]. The median survival time after recurrence was similar between the two groups, but the duration of DFS and OS were significantly higher in group B [ER(+)/PR(+)/HER2(-)]. Even though we do not know the level of HER-1, the negative effects of PR status on the prognosis of breast cancer may be related with the mechanisms mentioned above.

Results from a meta-analysis that evaluated the relationship between hormone receptor status (ER and PR) and response to hormonal therapy suggested that, while ER had a predictive value, PR had not. In contrast to the Oxford overview, claiming PR levels had no predicting value, several studies reported that PR status was an independent predictive factor for survival [5,17,18]. PR positivity not only in the adjuvant setting but also in the metastatic setting has been found to correlate with response to tamoxifen therapy. In a study of 342 assessable metastatic breast cancer patients treated with tamoxifen, increasing PR levels were associated with higher response rates to tamoxifen: for PR levels of <10, 10-99, and >100 fmol/mg, the response rates were 43, 53 and 61% respectively [19]. In the neoadjuvant setting, response to endocrine therapy and reduction in the proliferation rate seem to be better in PR(+) than in PR(-) tumors, whereas ER(+)/PR(-)/HER2(-) tumors have a better response to chemotherapy (higher pathological complete remission (pCR) rate) [6,20-22].

In the current study, we showed that the median DFS and OS were significantly worse and the risk of recurrence and death were higher in group A [ER(+)/PR(-)/HER2(-)]. This finding is consistent with the evidence supporting the impact of PR status on survival. Due to the small number of our patients given neoadjuvant treatment, statistical significance may not be found in this study.

In the large ATAC trial evaluating adjuvant hormonal therapy it was shown that ER(+)/PR(-) tumors had a higher recurrence rate in the tamoxifen and combination arm (14.8 vs 7.6%, respectively) [23]. This was because of the diminished efficiency of tamoxifen in PR(-) subgroup. But recurrence rates were similar in both ER(+)/PR(+) and ER(+)/PR(-) tumors that had only been treated with anastrozole.

In our study, death risk was found to be lower in patients treated with switch therapy or AI treatment (regardless of which type of aromatase inhibitor) in group A [ER(+)/PR(-)/HER2(-)]. This effect is probably due to ineffectiveness of tamoxifen in this group, but we do not know yet the exact mechanisms which may contribute to this result.

In this study we noticed some differences in the distributions of certain variables (menopausal status, stage, nodal involvement) in each groups, due rather to the retrospective nature of the study. Consistent with the literature [8], the ratio of postmenopausal patients was higher in group A. At the same time, group A included more lymph node negative and more stage I patients than group B; these might contribute to the better outcome in this patient group.

Also group A had less patients than group B, owing to the exclusion of stage 4 patients and the small number of patients.

In conclusion, even though there is sufficient amount of circulating estrogen and/or an active ER pathway, loss of PR occurs by means of different mechanisms, and the phenotype of the tumor [ER(+)/PR(-)/HER2(-)] has its own unwanted features. Despite the limitations of our study we hypothesize that PR negativity may be considered as a guide in the decision of administering hormonal therapy and chemotherapy regardless of menopausal status. Contrary to the standard hormonal therapy that includes tamoxifen, initiation with an AI as a first-line agent or a switch therapy with AI or keeping in mind that an extended adjuvant hormonal therapy might be an alternative option, may result in a better survival in ER(+)/PR(-)/HER2(-) patients.

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