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Original Article

Negative progesterone receptor status is an adverse prognostic factor for luminal B breast cancer

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Abstract: Progesterone receptor (PR) is involved in tumor but its prognostic value in breast cancer remains unclear. This study aimed to investigate whether PR status is a prognostic factor for luminal B breast cancer. Total 209 patients with invasive breast cancer were enrolled. We found that PR-negative luminal B breast cancer was significantly associated with older age. PR-negative subgroup showed significantly worse median disease-free survival (mDFS) than PR-positive subgroup with a hazard ratio (HR) of 1.80 (95% confidence interval [CI] 1.05-3.09). PR-negative subgroup also had an increased risk for non-visceral metastases (HR=2.17, 95% CI 1.09-4.31) as well as a trend toward higher risk for locoregional relapse (HR=2.23, 95% CI 0.95-5.26), compared to PR-positive subgroup. Furthermore, in HER2-negative patients, the HRs for mDFS, non-visceral metastases, and locoregional relapse were 2.54 (95% CI: 1.21-5.33), 2.79 (95% CI: 1.07-7.22), and 4.23 (95% CI: 1.34-13.40), respectively. Multivariate analysis showed that PR-negative status, lymph node positive cancer, and not receiving adjuvant radiotherapy were associated with reduced DFS and increased risk for non-visceral metastases and locoregional relapse. For patients with radiotherapy, PR-negative status remained a significant predictor of all outcomes, with HRs of 1.89 (95% CI: 1.11-3.21), 2.67 (95% CI: 1.36-5.24), and 2.47 (95% CI: 1.05-5.81) for DFS, non-visceral metastases, and locoregional relapse, respectively. In conclusion, PR-negative status is an independent adverse prognostic factor for luminal B breast cancer.

Keywords: Progesterone receptor, luminal B, breast cancer, prognostic factor

Introduction

Breast cancer is known to be a heterogeneous disease and can be divided into four molecular subtypes: luminal A, luminal B, HER2-enriched, and basal-like (triple negative) [1]. The evaluation of estrogen receptor (ER), progesterone receptor (PR), Ki-67, and HER2 by immunohistochemistry (IHC) has been used to identify the molecular subtypes of breast cancer [2, 3]. Luminal subtype breast cancers are proven to have better prognosis than HER2 and triple negative subtypes due to the expression of ER-associated genes and hormone receptor dependency. Luminal A is defined as ER-positive, PR-positive, HER2-negative, and low Ki-67 expression, and has the best prognosis of the four subtypes. However, luminal B breast cancer is more aggressive and is characterized by increased expression of HER2-associated genes, as well as high expression of a proliferation signature, including genes such as *CCNB1*, *MKI67*, and *MYBL* [4]. Moreover, compared to luminal A, luminal B subtype is more complicated and heterogeneous because it includes PR negative or positive and HER2 negative or positive patients and those with different Ki-67 levels, with various clinical disease courses and outcomes. Therefore, it is important to identify prognostic factors of luminal B breast cancer to achieve the best possible treatment for individual patients.

Young age, large tumor size, high tumor grade, lymphovascular invasion, cancer-positive lymph-nodes, cancer-positive margins, HER2 overexpression, and high recurrence risk based on multi-gene-expression assays, along with ER-negative/PR-negative status are generally considered poor prognosis factors for breast

cancer and have been used to guide clinical management [5]. However, the prognostic implication of PR in ER-positive/HER2-negative breast cancer remains unclear. Some studies indicated the possibility that low or negative expression of PR may be an independent prognosis factor in ER-positive breast cancer [6, 7]. However, these studies either focused on HER2-negative luminal B cohorts or undervalued the bias from the treatment of patient subgroups. In addition, little is known about the risk of visceral metastases.

Therefore, this study aimed to evaluate the prognostic implication of PR status in luminal B breast cancer by comparing both HER2-negative (luminal B1) and HER2-positive (luminal B2) subtypes. Because not all patients received treatments such as radiotherapy, we analyzed prognostic factors in subgroups receiving different treatments to avoid treatment bias.

Materials and methods

Patient selection and classification

The study cohort included 209 women with invasive breast cancer who received breast surgery at the Fujian Cancer Hospital, between January 2005 and June 2012. Male patients or patients with prior malignancy, synchronous bilateral breast cancer, and treatment with preoperative systemic therapy were excluded. Data on medical history, concurrent diseases, age, surgical information, pathological evaluation, and staging procedures such as chest radiographs or computed tomography (CT) scan, upper abdominal ultrasound examination, and bone scan were retrieved retrospectively.

We compared two subgroups of luminal B breast cancer: luminal B1 and luminal B2. In this study, luminal B1 was defined as ER positive, PR positive or negative, HER2 negative, as well as Ki-67≥14% (when PR is positive). Luminal B2 was defined as ER positive, PR positive or negative, HER2 positive (over-expressed and/or amplified), and any Ki-67 [8, 9]. ER-negative and PR-positive patients were excluded because many studies showed that there was actually no such phenotype in breast cancer [10, 11].

Tumors were classified histologically according to the World Health Organization Classification of Tumors [12]. Tumor staging was assessed according to the guide of American Joint Committee on Cancer (AJCC) [13].

Formalin-fixed, paraffin-embedded tissue samples were subjected to IHC staining for ER, PR, HER2, with primary antibodies against ER (SP1, Dako, Denmark), PR (PgR 636, Dako, Denmark), HER2 (4B5, Roche, Switzerland), and Ki67 (MIB-1, Dako, Denmark). IHC staining was routinely carried out by using Ventana BenchMark XT system (Ventana Medical Systems, Tucson, AZ, USA). All procedures were performed in the BenchMark automatically.

A fluorescence in situ hybridization (FISH) test for HER2 gene amplification was performed when HER2 was IHC 2+ by using the PathVysion HER-2 DNA FISH Kit (Vysis Inc, Downers Grove, IL) following the manufacturer's instructions.

ER and PR positive status was defined as the presence of greater than 1% of tumor cells with nuclear staining. Ki-67 index was expressed as the percentage of cells with positive nuclear staining among at least 1000 invasive cells in the area scored. HER2 over-expression (3+) was defined as complete and intense circumferential membrane staining of tumor cells. Tumor cells with weak to moderate circumferential membrane immunoreactivity were defined as HER2 (2+) and further examined by FISH for gene amplification. HER2 0 was defined as no staining, and 1+ was defined as incomplete membrane staining that was faint/barely perceptible and within >10% of the invasive tumor cells [14]. Patients were considered HER2-positive if they were either IHC 3+ or IHC 2+ with a FISH test showing HER-2 amplification.

Treatment

Of 209 patients, all of them received hormonal therapy and 207 patients received adjuvant chemotherapy. A total of 104 out of 209 patients received adjuvant radiation therapy, and 70 of 84 HER2-positive patients received adjuvant trastuzumab treatment.

Follow-up

Patients were followed up every 3 months after the completion of chemotherapy or radiotherapy. For patients lost to follow-up at our hospital, attempts were made to obtain information via telephonic contact. In total, 15 patients (7%) were lost to follow-up, and we censored these

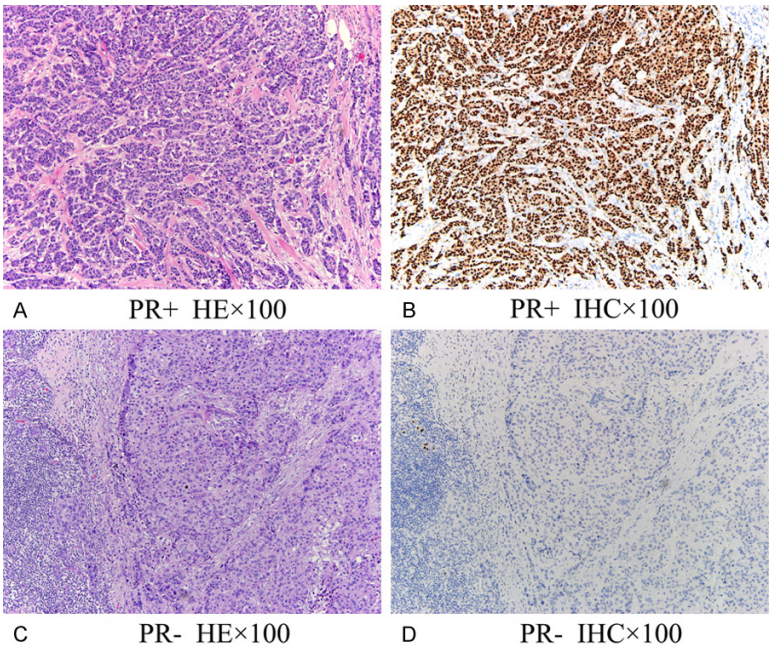

Figure 1. Histological and immunohistochemical analysis of breast cancer tiisues. A. HE staining of PR-positive tissue. B. PR staining of PR-positive tissue. C. HE staining of PR-negative tissue. D. PR staining of PR-negative tissue. Magnification: ×100.

patients in the analysis. Latest follow-up was at the end of December 2015. Median follow-up time was 31 months (range 1 to 109 months). Disease free survival (DFS) was defined as the time from the date of diagnosis to the first event (relapse or metastasis or death). This retrospective study has been approved by the Ethical Committees of Fujian Cancer Hospital.

Statistics

The chi-square test or the Fisher's exact test was used to assess the distribution of baseline characteristics between the PR-negative and PR-positive subgroups. Survival plots and cumulative incidences were drawn using the Kaplan-Meier method. The univariate analysis of the prognosis differences between the subgroups was conducted by using the Log-rank test. A Cox multivariate regression model was used to identify clinicopathological factors affecting the prognosis in the entire cohort and subgroups, using multivariate analysis. The major covariables were age, surgeon type, histologic type, tumor size, lymph node status, HER2 status, Ki-67% staining, radiotherapy, and trastuzumab treatment. Only patients with information for all of the covariates were included in the Cox regression analyses. Results that had *p*-value <0.05 were statistically significant. SPSS 19.0 software was used for statistical analysis.

The primary end-points were DFS, incidence of non-visceral metastases, visceral metastases, locoregional relapse, and distant metastases [15, 16]. Non-visceral metastasis is defined as cancer spread to the soft tissues, lymph nodes, or bone, while visceral metastasis involves the visceral organs, such as the liver, lung, brain, and pleura. Locoregional relapse is defined as breast cancer recurrence in the ipsilateral breast or axillary lymph nodes, or in the chest wall and skin of the ipsilateral breast. Distant metastases included all sites of recurrence except locoregional relapses and contralateral breast cancer as the first of subsequent events [17].

Results

Relationship between clinicopathologic characteristics and PR expression

Typical histological and immunohistochemical staining of PR-negative and PR-positive cancers were shown in **Figure 1**. Patients' characteristics are shown in **Table 1**. PR-negative luminal B breast cancer was associated with older age (48.5 *vs.* 43.0), and there were less young patients (<40 years) in the PR-negative subgroup than the PR-positive subgroup (18.0% *vs.* 37.1%). There was no correlation among PR status and surgeon type, histologic type, tumor size, lymph node status, TNM stage, HER2 status, or Ki-67% staining.

A total of 207 patients received chemotherapy and 104 (49.8%) patients received adjuvant radiotherapy, as well as 70 (33.5%) patients received adjuvant trastuzumab treatment across the entire cohort. No differences were observed in the distribution of adjuvant chemotherapy, adjuvant radiotherapy, and trastuzum-

Table 1. Baseline characteristics between PR negative and positive subgroups

Characteristics	PR negative N=50		PR positive N=159		*P*
	n	%	n	%	
Median age (y)	48.5 (46.8-52.3)		43.0 (42.8-45.5)		0.001
Young age (<40 y)					0.012
Yes	9	18.0	59	37.1	
No	41	82.0	100	62.9	
Surgeon type					0.544
Mastectomy	48	96.0	149	93.7	
Conservative	2	4.0	10	6.3	
Histologic type					0.769
Ductal	48	96.0	154	96.9	
Lobular	2	4.0	5	3.1	
Tumor size					0.650
T1	14	28.0	60	37.7	
T2	26	52.0	71	44.7	
T3	6	12.0	18	11.3	
T4	4	8.0	10	6.3	
Lymph node status					0.589
Negative	21	42.0	60	37.7	
Positive	29	58.0	99	62.3	
Positive lymph node numbers					0.552
0	21	42.0	60	37.7	
1-3	16	32.0	41	25.8	
4-9	7	14.0	35	22.0	
≥10	6	12.0	23	14.5	
TNM stage					0.670
I	9	18.0	34	21.4	
II	23	46.0	62	39.0	
III	18	36.0	63	39.6	
HER2 status					0.429
Negative	29	58.0	89	56.0	
Positive	18	36.0	66	41.5	
Unknown	3	6.0	4	2.5	
Ki-67% staining					0.265
<14	3	6.0	3	1.9	
14-35	24	48.0	63	39.6	
>35	18	36.0	74	46.5	
Unknown	5	10.0	19	12.0	
Adjuvant chemotherapy					0.422
Yes	49	98.0	158	99.4	
No	1	2.0	1	0.6	
Adjuvant radiotherapy					0.717
Yes	26	52.0	78	49.1	
No	24	48.0	81	50.9	
Trastuzumab treatment					0.798
Yes	16	32.0	54	34.0	
No	34	68.0	105	66.0	

ab treatment among the PR-negative and PR-positive subgroups.

Relationship between PR status and patient outcomes

On the univariate analysis, the PR-negative luminal B breast cancer subgroup showed worse DFS when compared to the PR-positive subgroup, with a mDFS of 45 months (95% CI: 33.8-56.2) *vs.* 65 months (95% CI: 47.8-82.2) (log-rank *P*=0.037), and a HR of 1.80 (95% CI 1.05-3.09) across the entire cohort. At 3 and 5 years, patients with PR-negative tumors had a DFS rate of 63.7% (95% CI: 49.6-77.8) and 37.0% (95% CI: 17.4-56.6), and patients with PR-positive tumors had a DFS rate of 70.2% (95% CI: 62.0-78.4) and 50.7% (95% CI: 39.1-62.3), respectively. Survival plots of the two subgroups are shown in **Figure 2**.

Moreover, the PR-negative subgroup had an increased risk for non-visceral metastases when compared to the PR-positive subgroup, with a HR of 2.17 (1.09-4.31) (*P*= 0.018) (**Figure 3**). There was no difference in risk for visceral metastases (*P*=0.685). As for the endpoints of locoregional relapse or distant metastases, the PR-negative subgroup showed a trend toward higher risk compared to the PR-positive subgroup, with a HR of 2.23 (0.95-5.26) for locoregional relapse (*P*=0.058)

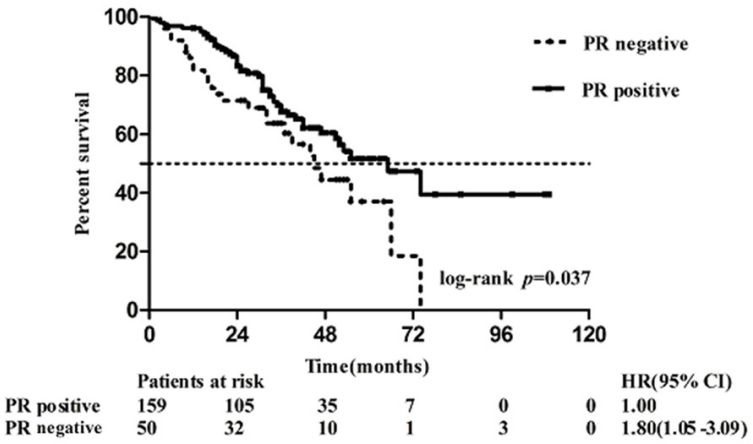

Figure 2. DFS of luminal B breast cancer according to PR status.

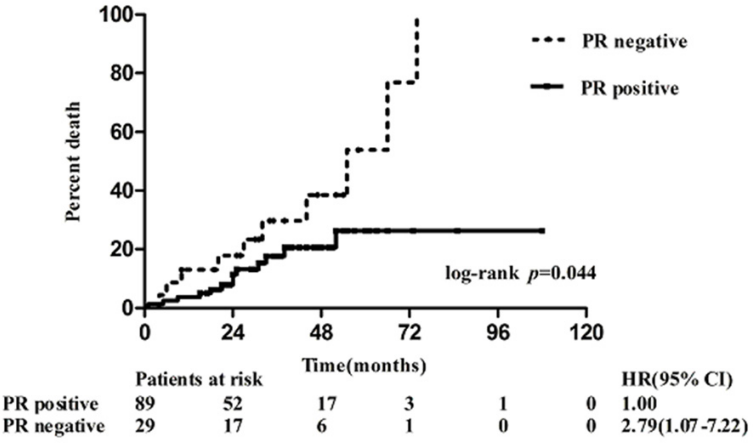

Figure 3. Non-visceral metastases in luminal B breast cancer according to PR status.

(**Figure 4**), but there was no difference in risk for distant metastases (*P*=0.251).

To further analyze the prognostic effect of PR, we divided the entire cohort into 2 subtypes: the luminal B1 subtype (HER2-negative) and the luminal B2 subtype (HER2-positive).

Among 118 HER2-negative patients, the PR-negative subgroup showed worse mDFS compared to the PR-positive subgroup, with a HR of 2.54 (95% CI: 1.21-5.33). The mDFS of the PR-negative subgroup was 45 months (95% CI 22.9-67.1), however the mDFS of the PR-positive subgroup was unreached (log-rank *P*=0.014) (**Figure 5**). In addition, the PR-negative subgroup showed a higher risk of non-visceral metastases when compared to the PR-positive subgroup, with a HR of 2.79 (95% CI 1.07-7.22) (*P*=0.044) (**Figure 6**). No differences between groups were observed for visceral metastases (*P*=0.159). Furthermore, the PR negative-subgroup had a higher risk of locoregional relapse when compared to the PR-positive subgroup, with a HR 4.23 (95% CI 1.34-13.40) (*P*=0.022) (**Figure 7**), but no differences between groups were observed for distant metastases (*P*=0.204).

For 84 HER2-positive patients (luminal B2 subtype), there was no difference in mDFS between the PR-negative and the PR-positive subgroups (log-rank *P*=0.803). There was also no difference in risk for non-visceral or visceral metastases (*P*=0.382, 0.506) or in risk for locoregional relapse or distant metastases (*P*=0.842, 0.873).

Multivariate analysis showed that PR-negative status (HR=1.89, 95% CI 1.11-3.21), lymph node positive status (HR=3.82, 95% CI 1.86-7.83), and not receiving adjuvant radiotherapy (HR=2.84, 95% CI 1.53-5.30) were parameters associated with an increased risk for worse DFS, as well as for non-visceral metastases and locoregional relapse. Tumor size had a marginal increased risk with respect to worse DFS, but not with respect to non-visceral metastases or locoregional relapse. However, Ki-67 (cutoff point 20%) seemed to be an insignificant covariate with all outcomes, including DFS, non-visceral metastases, and locoregional relapse (**Table 2**).

Since only some of the patients who were stage T3/4 or lymph node positive needed to receive radiotherapy, we further performed Cox analysis of patients who received radiotherapy to avoid treatment bias. PR-negative status remained a significant predictor of all outcomes considered in this subgroup, with HRs of 2.99 (95% CI 1.55-5.75), 3.76 (95% CI 1.71-8.25),

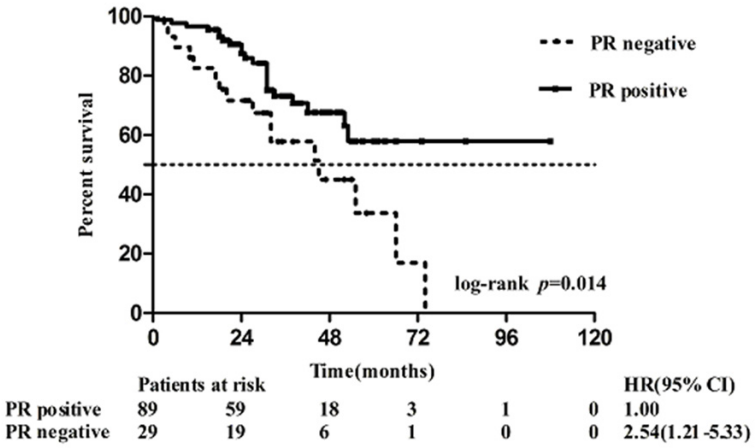

Figure 4. Locoregional relapse in luminal B breast cancer according to PR status.

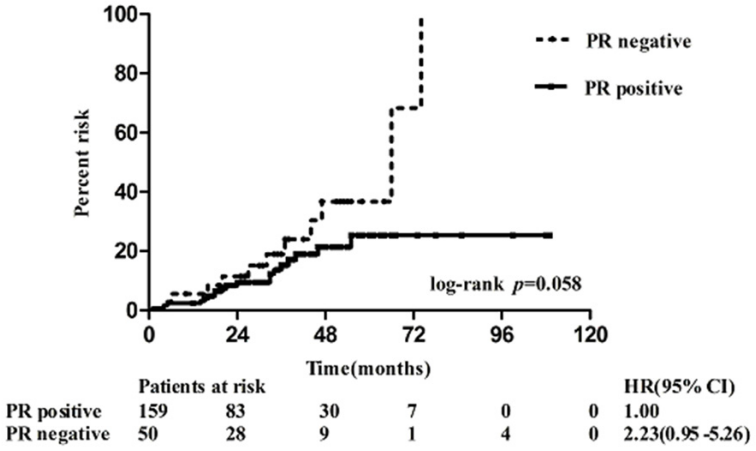

Figure 5. DFS of HER2-negative luminal B (luminal B1) breast cancer according to PR status.

and 6.32 (95% CI 2.11-18.88) for worse DFS, non-visceral metastases, and locoregional relapse, respectively. However, tumor size, Ki-67 status, and lymph node status did not increase the risk for worse DFS, non-visceral metastases, or locoregional relapse in patients who received radiotherapy (**Table 3**).

Discussion

It is widely accepted that different clinical and pathological characteristics combined with multi-parameter gene expression profiling provide useful prognostic information for patients with breast cancer [18-20]. Physicians should consider tailoring different treatments to various distinct subtypes of patients in order to make an appropriate therapeutic choice.

However, of the four subtypes of breast cancer, luminal B is the most heterogeneous, comprising a group of patients with ER-positive, PR positive or negative, HER2 positive or negative, and different Ki-67 level statuses. Endocrine therapy is essential for the luminal B subtype, and trastuzumab is needed for patients with HER2-positive status. However, there is still a lack of consensus about using chemotherapy for patients with luminal B cancer. It is important to find prognostic factors that will help physicians chose treatment for this subtype. Here we focus on PR status, which may have prognostic significance [21].

Previous studies have shown that PR-negative breast cancers are more frequent in postmenopausal patients [22]. In our study, we also find PR-positive expression is more likely in young women. Distributions of other baseline characteristics between PR-negative and PR-positive groups show no difference, which indicates that the characteristics are tolerably balanced between the two subgroups. PR is an ER-induced gene target, so the different distribution of PR may be due to estrogen-mediated PR transcriptional activity caused by high level of estrogen in young women [23, 24].

However, whether PR is a prognostic factor still remains unclear because different studies show inconsistent results. Cuzick et al. showed that PR-negative status was a poor prognostic factor for distant recurrences in both univariate and multivariate analysis models [3]. Other studies reported that PR negativity was significantly associated with a poor prognosis in luminal B breast cancer, mostly in HER2-negative subgroup [6, 25], but another study did not support that PR was one of the adverse prognostic factors for breast cancer [26].

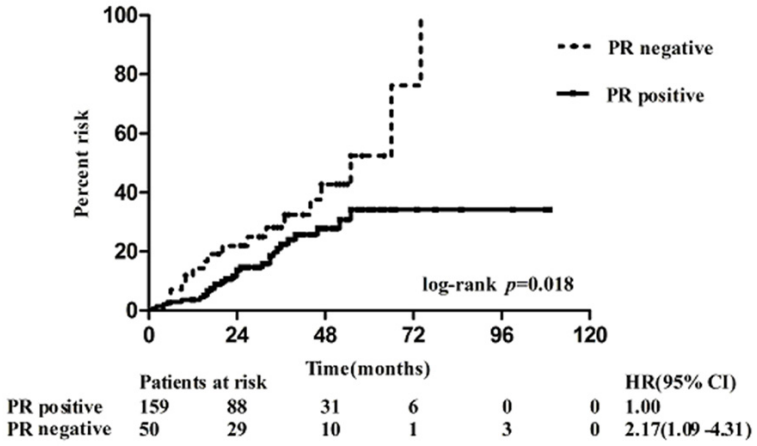

Figure 6. Non-visceral metastases in HER2-negative luminal B (luminal B1) breast cancer according to PR status.

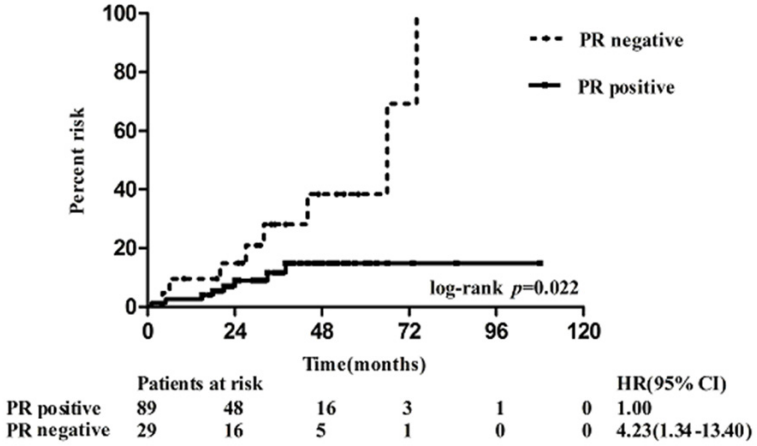

Figure 7. Locoregional relapse in HER2-negative luminal B (luminal B1) breast cancer according to PR status.

From the univariate analysis in our study, we observed that PR-negative patients had poorer survival than PR-positive patients did, across the luminal B cohort (HR 1.80, 95% CI 1.05-3.09), but particularly in the luminal B1 subtype (HR 2.54, 95% CI 1.21-5.33) rather than the luminal B2 subtype. Increased risk of non-visceral metastases and locoregional relapse were also observed in the PR-negative luminal B1 subtype. These results are consistent with previous studies [6, 25]. For those patients with luminal B2 subtype, the prognostic role of PR may be weaken by an over-activated HER2 pathway, which down-regulates PR expression [22, 27].

Furthermore, our study suggests that PR is an important independent prognostic factor, and that performing multivariate analysis could properly define subgroups with distinct prognoses in luminal B breast cancer patients to inform treatment choices. Other poor prognostic factors include positive lymph nodes and not receiving adjuvant radiotherapy. In addition, our data show that PR-negative status indicates a higher risk of non-visceral metastases and locoregional relapse, which is seldom reported in other papers. It has been confirmed that the survival time is lower for patients who develop visceral metastases or distant recurrences than those who develop non-visceral metastases or local relapse, and those with visceral metastases are often regarded as less likely to respond to hormonal therapy than those with non-visceral metastases; consequently such patients tend to receive chemotherapy [28]. This may explain why a PR-negative status modestly increases the risk when compared with the presence of positive lymph nodes or having received radiotherapy.

To avoid the bias of adjuvant radiotherapy, which is only needed in particular patient groups, but not in the entire cohort, multivariate Cox's analysis was performed for patients who received radiotherapy. The results showed that PR status is the only prognostic factor in luminal B breast cancer. PR mediates progesterone's effects on the development of mammary gland and breast cancer [29]. The predictive value of PR has been described as the dependence of PR expression on a functional ER and PR pathway, and the loss of PR indicates nonfunctional ER signaling and resistance to hormonal therapy [30, 31]. Other studies indicate that ER down-regulates PR expression through crosstalking with other signaling pathways. Previous studies have also shown that high growth factor signaling may be associated with decreased PR expression through the PI3K/Akt/mTOR signal-

Table 2. Multivariate analysis for DFS, non-visceral metastases and locoregional relapse in luminal B breast cancer patients

Risk factor	DFS			Non-visceral metastases			Locoregional relapse		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
PR			0.020			0.004			0.039
Positive	1.00	-		1.00	-		1.00	-	
Negative	1.89	1.11-3.21		2.67	1.36-5.24		2.47	1.05-5.81	
Ki-67 staining			0.086			0.122			0.188
<20%	1.00	-		1.00	-		1.00	-	
≥20%	2.26	0.89-5.70		3.11	0.74-13.13		3.89	0.51-29.38	
Tumor size			0.055			0.120			0.288
T1-2	1.00	-		1.00	-		1.00	-	
T3-4	1.85	0.99-3.45		1.91	0.85-4.30		1.78	0.62-5.14	
Lymph node status			0.001			0.003			0.001
Negative	1.00	-		1.00	-		1.00	-	
Positive	3.82	1.86-7.83		4.60	1.69-12.52		7.90	2.32-26.90	
Adjuvant radiotherapy			0.001			0.044			0.009
Yes	1.00	-		1.00	-		1.00	-	
No	2.84	1.53-5.30		2.29	1.02-5.15		3.58	1.38-9.27	

Table 3. Multivariate analysis for DFS, non-visceral metastases and locoregional relapse in luminal B breast cance patients with adjuvant radiotherapy

Risk factor	DFS			Non-visceral metastases			Locoregional relapse		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
PR			0.001			0.001			0.001
Positive	1.00	-		1.00	-		1.00	-	
Negative	2.99	1.55-5.75		3.76	1.71-8.25		6.32	2.11-18.88	
Ki-67 staining			0.093			0.101			0.204
<20%	1.00	-		1.00	-		1.00	-	
≥20%	1.93	0.90-4.15		2.06	0.87-4.90		2.14	0.66-6.91	
Tumor size			0.057			0.118			0.177
T1-2	1.00	-		1.00	-		1.00	-	
T3-4	1.98	0.98-4.00		2.05	0.83-5.05		2.45	0.69-8.98	
Lymph node status			0.262			0.475			0.919
Negative	1.00	-		1.00	-		1.00	-	
Positive	3.14	0.43-23.22		2.09	0.28-15.82		1.11	0.14-8.94	

ing cascade [22, 32], Loss of Phosphatase and tensin homolog (PTEN), which is a negative regulator of this pathway, is also associated with down-regulation of PR [33]. More recently, data show that PR can interact with ER by re-directing ER chromatin binding and altering the expression of target genes, which is associated with low tumorgenicity and better prognosis [21].

Hence, increases in growth factor activity may be a mechanism that results in ER-positive/PR-negative breast cancer and causes anti-estrogen therapy resistance or insensitivity. Combination use of anti-estrogen therapy (e.g. TAM, aromatase inhibitors, fulvestrant, or ovarian ablation) and mTOR inhibitor (e.g. everolimus) or PIK3CA inhibitors may be a promising solution [34-36]. In contrast, anti-estrogen therapy combined with native progesterone may improve drug efficacy in ER-positive/PR-positive breast cancer [37].

There are several limitations to this study. First, it is a retrospective analysis and must be interpreted with caution because of the increased

likelihood of false-positive and false-negative results. Second, the sample size of this study is not enough to draw a convincing result, and the relatively small numbers in certain subgroups widens the CIs of the outcomes. Last, the St. Gallen Consensus has considered PR expression cutoff values as high as 20% to redefine the luminal A subtype since 2013 [8]. Since all the patients in this study cohort received a therapeutic regimen based on recommendations from the 2011 St. Gallen Consensus, we did not use the new definition of luminal B tumors in order to avoid bias in this retrospective study. Our result may still be meaningful because the new definition increases the luminal B breast cancer population, but the best way to find out is to conduct further research.

In summary, this study suggests that PR is an independent adverse prognostic factor for DFS and is significantly associated with both increased non-visceral metastases and locoregional relapse risk in patients with luminal B breast cancer. Although expansion of the cohort and longer follow-up is needed, our results may be useful in counseling individual patients with luminal B breast cancer about their treatment options.

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Disclosure of conflict of interest

None.

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