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Prognostic Factors for Luminal B-like Breast Cancer*

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Summary: This study aimed to examine the prognostic factors of luminal B-like breast cancer. Clinical data of 695 luminal B-like breast cancer patients who had been treated in our hospital during the period of past 4.5 years were collected and analyzed. Estrogen receptor (ER), progesterone receptor (PgR), antigen identified by monoclonal antibody Ki-67 (Ki67) were immunohistochemically detected. Different cutoffs of ER, PgR, and Ki67 were evaluated. Pearson χ^2 test was performed to compare categorical parameters. Univariate and multivariate models were used to evaluate predictors of disease free survival (DFS). The results showed that patients who were younger, and had larger tumors, and more positive lymph nodes were more likely to receive neo-adjuvent chemotherapy (NAC). Patients with ER-positive tumors having <10% positive cells received more anthracycline- and taxane-based chemotherapy and less endocrine therapy than those with ER-positive tumors having ≥10% positive cells (P=0.004 and P=0.007, respectively); however, patients with ER-positive tumors having <10% positive cells experienced more recurrence (P<0.001). PgR expression levels were not associated with therapeutic schedule and DFS. Patients with tumor tissue Ki67 score ≥30% received more anthracycline- and taxane-based chemotherapy and had worse DFS than those with tumor tissue Ki67 score <30%. Univariate and multivariate analysis showed that clinical T stage, lymph nodes, ER, Ki67, and HER2 status were independent prognostic factors. In conclusion, ER-positive rate <10% and Ki67 score ≥30%, similar to higher clinical T stage, more metastatic lymph nodes, and HER2 positive status, may indicate a worse prognosis for luminal B-like breast cancer patients. Multi-center prospective trials with larger sample sizes are necessary for the continued perfection of our work.
Key words: luminal B-like breast cancer; threshold; prognostic factor; estrogen receptor; Ki67

According to the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2013, the surrogate definition of intrinsic luminal B subtype breast cancer included the following: (for HER2 negative) estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative and high monoclonal antibody Ki-67 (Ki67)/ progesterone receptor (PgR) negative or low/high recurrence risk; (for HER2 positive) ER positive, HER2 over-expressed or amplified, regardless of Ki67 score and PgR value[1]. In 2010, guidelines from the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) recommended that ER status should be considered positive if 1% or more of tumor cells demonstrate ER-positive nuclear staining on immunohistochemistry (IHC)[2]. More patients would receive endocrine therapy due to the decrease of ER positive thresholds; before the ASCO/CAP guideline, many clinicians considered patients with tumor cell ER-positive rate ≥10% as positive and eligible for endocrine therapy[3, 4]. For the expression level of PgR, the cutoff of 20% was viewed as optimal by adding prognostic value within IHC-based luminal A tumors[5]. Nevertheless, some clinicians found that patients with PgR negative tumors had a worse prognosis than those with PgR positive[6, 7]. In terms of proliferation marker Ki67, the heterogeneity of breast tumors and different laboratory protocols make it difficult to come to an agreement regarding thresholds[8], although great efforts have been made to improve the concordance of Ki67 scoring[9, 10]. Compared to patients with luminal A tumors, those with luminal B tumors have worse prognoses and may benefit from chemotherapy[11]. Nevertheless, little research has been done to address the following question: which type of these luminal B-like patients would be sensitive to chemotherapy and endocrine therapies, based on the large range of ER/ PgR/Ki67 values. In this study, in order to find suitable cutoffs for luminal B-like patients, we compared the disease free survival (DFS) among these patients with different cutoff values of ER, PgR, Ki67. HER2 status

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and usage of neo-adjuvent chemotherapy (NAC) were also evaluated.

1 PATIENTS AND METHODS

A total of 1350 consecutive cases of primary invasive breast cancer diagnosed and treated at Central South University Xiangya Hospital Breast Cancer Center between June 2010 and December 2014 were reviewed. Patients with primary metastasis disease, inflammatory disease or pregnant women were excluded from this study. All patients were from a Chinese population and were female. Characteristic records of patients and tumors were obtained from hospital medical records, including age at diagnosis, clinical TNM stage, systemic chemotherapy regimen, histological grade, ER status, PgR status, Ki67 and HER2 status. HER2 positive was defined as IHC staining of 3+ or IHC staining of 2+ and FISH (+, HER2/CEP17 ration >2.2). Pathological complete response (pCR) was defined as no pathological evidence of a residual invasive carcinoma in the breast or axillary lymph nodes. Residual ductal carcinoma in situ (DCIS) was included in pCR.

Within the whole sample, 716 patients received NAC, and 634 patients underwent surgery before chemotherapy. Based on the St. Gallen consensus 2013[1], patients were grouped into four subtypes: luminal A-like (226 patients), triple negative (216 patients), HER2 positive (109 patients) and luminal B-like (725 patients). A total of 74 patients were excluded because of unknown of HER2 status. Thirty patients of the luminal B-like subtype were also excluded due to less than 3 months of follow-up time. Overall, 695 patients were evaluated for age, clinical T stage, lymph nodes, histological grade, ER/PgR/Ki67/HER2 status and DFS (fig. 1). The median length of follow-up was 35 months (range: 5 to 77 months). The study was approved by the Institutional Review Board of Xiangya Hospital of Central-South University.

Pearson χ^2 test or Fisher's exact test was performed to compare categorical parameters of clinicopathological characteristics. Wilcoxon scores rank sum test was used for independent samples. For the survival analyses, the endpoint was DFS. DFS was defined as time from date of surgery to date of first relapse (local or distant) or secondary primary malignancy. Kaplan-Meier curves and log-rank test were performed to assess differences among groups. Multivariate Cox regression models were established to identify significant predictors of DFS. Statistical significance was calculated at the 95% confidence interval (P<0.05), and all analysis was carried out using SPSS version 17.0 for Windows (SPSS Inc, USA) like we did before[12].

2 RESULTS

2.1 Clinical and Pathological Characteristics of Patients

Out of the 695 patients included in this study, the median age at diagnosis was 46 years (mean 47.5, range: 23-81), and 473 (68.1%) patients were younger than 50 years old. Patients and tumor characteristics are summarized in table 1. Patients who were younger, with larger tumors and more positive lymph nodes, were more likely to receive NAC. Compared with patients who did not receive NAC, those receiving NAC were more likely to be younger than 50 years old (73.1% *versus* 62.5%, P=0.003), and more likely to have advanced disease (clinical stage T2-4 93.1% *versus* 70.7%, P<0.001) with more lymph nodes metastasis (53.7% *versus* 44.3%, P=0.001). Their ER-positive tumors more likely had <10% positive cells (13.9% *versus* 7.5%, P=0.007). The PgR, Ki67 and HER2 status were similar when comparing patients

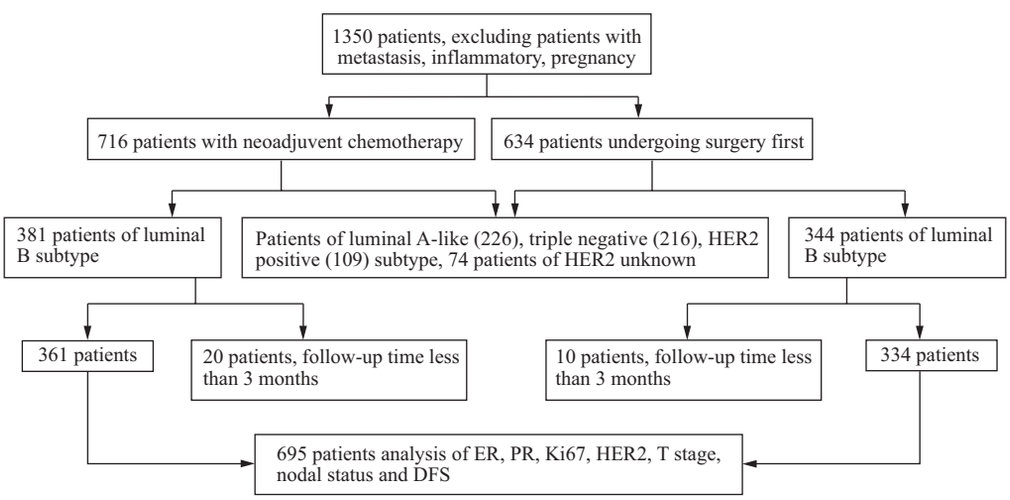

Fig. 1 Grouping of the patients and the final number of study subjects

with NAC to those without NAC. Of the 361 patients who received NAC, 42 (11.6%) patients had reached pCR.

Table 1 Clinicopathological characteristics of the patients [*n* (%)]

Factors	Neu-adjuvent chemotherapy		*P* value
	No (*n*=334)	Yes (*n*=361)	
Age (years)			
Mean	49.1	46	0.003*
Median (range)	47 (23–81)	45 (26–66)	
Age distribution			
≤50 years	209 (62.6)	264 (73.1)	0.003
>50 years	125 (37.4)	97 (26.9)	
Clinical T stage			
T1	98 (29.3)	25 (6.9)	
T2	228 (68.3)	214 (59.3)	<0.001
T3	4 (1.2)	86 (23.8)	
T4	4 (1.2)	36 (10)	
Lymph nodes (positive number)			
0	186 (55.7)	167 (46.3)	
1–3	106 (31.7)	109 (30.2)	0.001
≥4	42 (12.6)	85 (23.5)	
Histological grade			
1–2	256 (76.6)	309 (85.6)	0.003
3	78 (23.4)	52 (14.4)	
ER (%)			
<10	25 (7.5)	50 (13.9)	0.007
≥10	309 (92.5)	311 (86.1)	
PgR (%)			
<20	190 (56.9)	222 (61.5)	0.217
≥20	144 (43.1)	139 (38.5)	
Ki67 (%)			
<30	184 (55.1)	177 (49.0)	0.110
≥30	150 (44.9)	184 (51.0)	
HER2 status			
Negative	262 (78.4)	279 (77.3)	0.713
Positive	72 (21.6)	82 (22.7)	
pCR			
Yes	–	42 (11.6)	
No	–	319 (88.4)	

*: Wilcoxon scores rank sum test

2.2 Adjuvant Therapy, Follow-up and Recurrence Status among Patients

Therapy, follow-up and recurrence status among patients are shown in table 2 and table 3. Data were shown by using cutoffs of ER (10%), PgR (20%) and Ki67 (30%). Overall, 10.8% (75) of patients had tumors with ER-positive rate<10%, 59.3% (412) of patients had tumors with PgR-positive rate<20%, and 51.9% (361) of patients had tumors with Ki67 score <30%. Compared with patients with tumor cell ER-positive rate≥10%, those with tumor cell ER-positive rate<10% were more likely to receive anthracycline- and taxane-based chemotherapy (97.3% *versus* 81.6%, *P*=0.004) and less likely to receive regular adjuvant endocrine therapy (80% *versus* 91.1%, *P*=0.007). The expression levels of PgR were not significantly associated with the chemotherapy regimens, adjuvant endocrine or radiation therapy when a cutoff value of 20% for PgR expression was used. Patients with tumor Ki67 score ≥30% were more likely to receive anthracycline- and taxane-based chemotherapy (90.4% *versus* 76.7%, *P*<0.001) and less likely to have regular adjuvant endocrine therapy (87.1% *versus* 92.5%, *P*=0.016) than patients with tumor Ki67 score <30%. The ER, PgR, and Ki67 status of patients were not significantly associated with reception of radiation therapy. Patients with tumor cell ER-positive rate≥10% and Ki67 score <30% had longer follow-up time. Patients with tumor cell ER-positive rate<10% were more likely to experience recurrences than those with tumor cell ER-positive rate≥10%, including total, local and distant recurrences (*P*<0.001, *P*=0.003 and *P*=0.027, respectively). There were no significant differences in local, distant and total recurrences between patients with different PgR status. Compared to patients with tumor Ki67 score <30%, those with tumor Ki67 score ≥30% were more likely to experience total and local recurrences (14.7% *versus* 8.6%, *P*=0.012 and 5.4% *versus* 1.9%, *P*=0.015, respectively), but not distant recurrences (11.1% *versus* 7.2%, *P*=0.075). Overall, 22.2% (154) of patients had tumors with positive HER2, and 27.3% (42) of these HER2-positive patients received Herceptin treatment. Patients who had received Herceptin treatment were less likely than those without Herceptin therapy to experience total and distant recurrences (4.8% *versus* 25%, *P*=0.005 and 4.8% *versus* 22.3%, *P*=0.011, respectively), but not local recurrences (*P*=0.190).

2.3 DFS Outcomes

Kaplan-Meier curves were used for the analysis of outcomes in different groups. At a median follow-up of 35 (5–77) months, patients with NAC or tumor Ki67 score≥30% had worse DFS rate than those without NAC or with tumor Ki67 score<30% (*P*=0.01 and *P*=0.001, respectively, fig. 2A and 2B). As shown in fig. 2C and 2D, patients with large tumor size or more lymph nodes metastasis experienced more recurrences than those with small tumor or less/no lymph node metastasis (both *P*<0.001). DFS outcomes comparing patients with tumor ER-positive rate<10% and ER-positive rate≥10% are shown in fig. 2E (total patients) and fig. 2F (patients with endocrine therapy). Patients with tumor ER-positive rate≥10% had better DFS rate than those with tumor ER-positive rate<10% , regardless of endocrine therapy use (both *P*<0.001). Patients with HER2 positive tumors had worse DFS rates compared to those with HER2 negative tumor (*P*<0.001, fig. 2G). The DFS rate was improved for HER2-positive patients who had Herceptin treatment compared to those without Herceptin treatment (*P*=0.002, fig. 2H). Patients in different age groups (<50 years *versus* ≥50 years),

Table 2 Therapy and recurrence status among the patients [*n* (%)]

Factors	ER (%)		*P* value	PgR (%)		*P* value	Ki67 (%)		*P* value
	<10 (*n*=75)	≥10 (*n*=620)		<20 (*n*=412)	≥20 (*n*=283)		<30 (*n*=361)	≥30 (*n*=334)	
Chemotherapy									
Yes (A* or TΔ-based)	2 (2.7)	74 (11.9)		47 (11.4)	29 (10.2)		58 (16.1)	18 (5.4)	
Yes (A* and TΔ-based)	73 (97.3)	506 (81.6)	0.004#	339 (82.3)	240 (84.4)	0.652	277 (76.7)	302 (90.4)	<0.001
Not completed	0	19 (3.1)		11 (2.7)	8 (2.8)		10 (2.8)	9 (2.7)	
No	0	21 (3.4)		15 (3.6)	6 (2.1)		16 (4.4)	5 (1.5)	
Endocrine therapy									
Regular	60 (80)	565 (91.1)		372 (90.3)	252 (89.4)		334 (92.5)	291 (87.1)	
Irregular	11 (14.7)	35 (5.6)	0.007#	29 (7)	17 (6)	0.353	21 (5.8)	25 (7.5)	0.016
No	4 (5.3)	20 (3.2)		11 (2.7)	13 (4.6)		6 (1.7)	18 (5.4)	
Radiation therapy									
Yes	25 (39.7)	174 (30.7)		117 (31.5)	82 (31.8)		97 (29.7)	102 (33.8)	
No	38 (60.3)	392 (69.3)	0.148	254 (68.5)	176 (68.2)	0.948	230 (70.3)	200 (66.2)	0.268
Unknown	12	54		41	25		34	32	
Follow-up (months)									
Mean	30.8	36.9	0.004**	36.9	35.3	0.288**	39.2	33.0	<0.001**
Median (range)	28 (6–72)	35 (5–77)		35 (5–76)	33 (6–77)		38 (5–76)	30 (6–77)	
Total recurrence									
Yes	20 (26.7)	60 (9.7)	<0.001	55 (13.3)	25 (8.8)	0.067	31 (8.6)	49 (14.7)	0.012
No	55 (73.3)	560 (90.3)		357 (86.7)	258 (91.2)		330 (91.4)	285 (85.3)	
Local recurrence									
Yes	8 (10.7)	17 (2.7)	0.003#	16 (3.9)	9 (3.2)	0.625	7 (1.9)	18 (5.4)	0.015
No	67 (89.3)	603 (97.3)		396 (96.1)	274 (96.8)		354 (98.1)	316 (94.6)	
Distant recurrence									
Yes	12 (16)	51 (8.2)	0.027	43 (10.4)	20 (7.1)	0.128	26 (7.2)	37 (11.1)	0.075
No	63 (84)	569 (91.8)		369 (89.6)	263 (92.9)		335 (92.8)	297 (88.9)	

*: anthracycline; Δ: taxane; #: Fisher's exact test; **: Wilcoxon scores rank sum test

Table 3 Follow-up and recurrence status among HER2 positive patients treated with Herceptin or not

Factors	HER2 Positive (*n*=154)		*P* value
	Herceptin (+, *n*=42)	Herceptin (–, *n*=112)	
Follow-up (months)			
Mean	36.1	28.7	0.001*
Median (range)	35 (14–69)	27 (5–76)	
Total recurrence			
Yes	2 (4.8)	28 (25)	0.005
No	40 (95.2)	84 (75)	
Local recurrence			
Yes	0 (0)	6 (5.4)	0.190Δ
No	42 (100)	106 (94.6)	
Distant recurrence			
Yes	2 (4.8)	25 (22.3)	0.011
No	40 (95.2)	87 (77.7)	

*: Wilcoxon scores rank sum test; Δ: Fisher's exact test

histological grade groups (grade 1–2 *versus* grade 3), and PgR groups (<20% *versus* ≥20%) did not show significant differences in DFS rates (data not shown).

Cox regression model was used for the evaluation of DFS rates among overall patients, including the 6 possible factors of NAC, clinical T stage, lymph nodes, ER, Ki67, and HER2 status. As shown in the table 4, clinical T stage, lymph nodes, ER, Ki67, and HER2 status were independent prognostic factors, but NAC was not.

Table 4 Cox regression model for DFS among overall patients

Factors	HR	SE	*P* value	95% CI
NAC				
No	Reference			
Yes	1.064	0.262	0.814	0.637–1.776
Clinical T stage				
T1	Reference			
T2	3.332	0.600	0.055	0.976–10.250
T3	4.579	0.636	0.016	1.332–16.079
T4	9.010	0.652	0.001	2.370–30.532
Lymph nodes				
0	Reference			
1–3	2.400	0.303	0.004	1.326–4.343
≥4	4.839	0.290	<0.001	2.739–8.550
ER (%)				
<10	Reference			
≥10	0.407	0.283	0.001	0.234–0.709
Ki67 (%)				
<30	Reference			
≥30	1.892	0.234	0.006	1.197–2.992
HER2 status				
Negative	Reference			
Positive	1.908	0.249	0.009	1.172–3.106

HR: hazard ratio; SE: standard error; CI: confidence interval

3 DISCUSSION

Luminal B subtype breast cancer usually benefited from chemotherapy if patients had a high recurrence

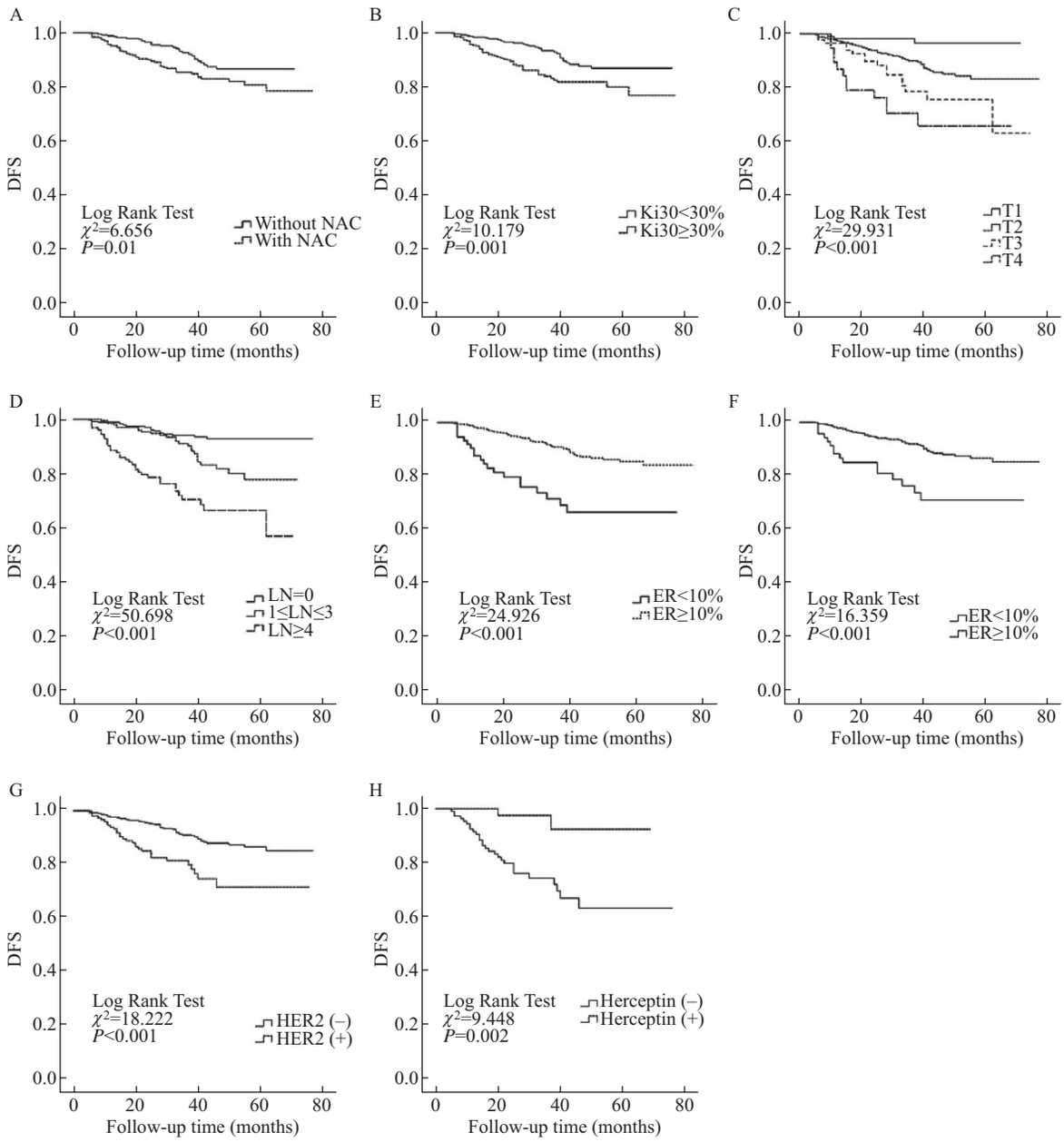

Fig. 2 Kaplan-Meier curves were used for the analysis of disease free survival (DFS) outcomes
A: Patients with NAC had worse DFS rate than those without NAC. B: Patients with tumor Ki67 score ≥30% had worse DFS rate than those with tumor Ki67 score <30%. C: Patients with larger tumor size experienced higher recurrence rate than those with small tumor. D: Patients with more lymph nodes metastasis had lower DFS rate than those with less/no lymph node metastasis. E: Patients with tumor cell ER-positive rate ≥10% had better DFS rate than those with tumor cell ER-positive rate <10% in the total patients group. F: Patients with tumor cell ER-positive rate ≥10% had higher DFS rate than those with tumor ER-positive rate <10% in the group of patients with endocrine therapy. G: Patients with HER2 positive tumors had lower DFS rates than those with HER2 negative tumor. H: The DFS rate was improved for HER2-positive patients with Herceptin treatment compared to those without Herceptin treatment.

score[13,14]; however, few studies attempted to determine whether or not the additional survival benefit of NAC existed when compared to adjuvant chemotherapy. In this study, patients with NAC seemed to have worse DFS rates than those with adjuvant chemotherapy. In multivariate analysis, however, chemotherapy before or after surgery did not additionally influence the outcome. This may be due to the retrospective nature of this study, in which patients with larger tumors, with tumor cell ER-positive rate<10%, and with more metastatic lymph nodes were more likely to receive NAC. Despite this unbalance, these three factors were independent prognostic factors and influenced outcomes. The pCR is viewed as a predictor of NAC sensitivity, while luminal B subtype tumors exhibit lower pCR rates than HER2-enriched and triple-negative breast tumors[15, 16]. Even when compared to luminal A tumors, luminal B tumors were not

homogenously observed to have higher pCR rates[15, 17]. In this study, 11.6% (42) of patients with NAC had reached pCR, which is comparable to the results from other studies[16, 18]; nevertheless, survival benefit (significantly increased DFS) was not observed in patients who had obtained pCR in our study (data not shown). Prospective randomized trials are needed for a more reliable conclusion.

ER is a prognostic factor for breast cancer and a predictor of response to endocrine therapy. Our study shows that approximately 10.8% (75) of luminal B-like patients had a tumor cell ER-positive rate<10%, and these patients had worse prognoses than those with tumor ER-positive rate≥10%. In this study, most of the luminal B-like patients had received anthracycline- and taxane-based chemotherapy, which was recommended by the 2011 St. Gallen consensus[19]. Considering the weaker response to endocrine therapy and the worse prognoses of patients with tumor ER-positive rate<10%, these patients were more likely to receive anthracycline- and taxane-based chemotherapy than those with tumor cell ER-positive rate≥10%. Overall, 89.9% of patients had followed clinicians suggestion of receiving regular endocrine therapy, and patients with tumor cell ER-positive rate<10% did not appear to have benefited from endocrine therapy. Our results are in line with previous findings which showed the significant association between low-ER positive status and poor survival outcome[20–22]. Recently, a study that examined the biology characteristics and clinical behavior of breast tumors with low ER levels (1%–9%) indicated that the survival of patients with low ER expression are intermediate between that of ER-positive rate>10% group and ER negative groups[20]. Reports from large cohort and meta-analysis showed that tumors with low ER expression behave worse than those with high ER expression[21, 22].

The prognostic value of PgR was mostly confirmed in population-based studies[5, 6], yet few studies have evaluated its significance in luminal B-like breast tumors. In this study, 10.5% (73) of patients had PgR negative tumors; 59.3% (412) of patients had tumors with PgR-positive rate<20%. We have attempted to determine whether PgR expression levels could predict risks of recurrence in luminal B-like tumors. Different cutoffs were evaluated, yet a significant difference between groups was not observed. Patients with tumor PgR-positive rate<20% were more likely to experience total recurrence than those with PgR positive ≥20% (P=0.067). Recently, a patient-level meta-analysis of randomized trials from the Early Breast Cancer Trialists' Collaborative Group evaluated 5 years of treatment with tamoxifen *versus* no tamoxifen therapy; and results indicated that recurrence and death were not associated with PgR status in ER-positive breast cancer[22]. In addition, in two large adjuvant clinical trials that evaluated the endocrine benefit of aromatase inhibitor *versus* tamoxifen, the predictive significance of PgR expression levels were not observed[4, 23]. Overall, these data suggest PgR expression levels have less impact than ER expression levels on the outcome of luminal B-like patients.

The prognostic value of Ki67 was supported by extensive studies, but cutoffs to distinguish "high" from "low" varied from 1% to 28.6%[24]. An optical cutoff appears to be different between laboratories[25]. In this study, the most commonly used cutoffs (14% or 20% or 30%) have been validated to search for a suitable cutoff for our center. The results show that a cutoff of 30% could separate luminal B-like patients into two distinct groups, and patients with tumor Ki67 score ≥30% would be more likely to experience recurrence when compared to those with tumor Ki67 score <30%, even though they were more likely to receive anthracycline- and taxane-based chemotherapy. This threshold was also verified to be an independent prognostic factor in the multivariate analysis. This might be helpful for other laboratories; however, without standardization of methodology among different laboratories, the clinical utility is limited.

In terms of clinical tumor T stages, number of metastatic lymph nodes, and HER2 status, our study shows that these factors are independent survival predictors in luminal B-like patients. All of these factors have been suggested as predictors in extensive studies and guidelines in unselected breast cancer patients[25, 26]. Patients who have received Herceptin treatment were less likely to experience total recurrence, especially distant recurrence, compared to those without Herceptin therapy. Unfortunately, only 27.3% (42) of patients with HER2-positive tumors underwent anti-HER2 therapy because of economic issues.

The current study has limitations. First, this is a single-center clinical retrospective study, which limits the randomization. Multi-center prospective control trials are necessary for a more reliable conclusion. Second, because of the limited sample size of patients, we cannot perform subset analyses based on different regimens of chemotherapy and endocrine therapy. Third, Chinese herbal medicine has been widely used in our population, and there are distinctions among different prescriptions of herbal medicine. We cannot account for differences in the way these herbal medicine regimens may affect results.

In conclusion, ER-positive rate<10% and Ki67 score ≥30%, similar to higher clinical T stage, more metastatic lymph nodes, and HER2 positive status, might indicate a worse prognosis for luminal B-like breast cancer patients. The expression levels of PgR might be not associated with recurrence in these subtype patients. Multi-center prospective trials with larger sample sizes are necessary for the continued

perfection of our work.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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