Prognostic effect analysis of molecular subtype on young breast cancer patients

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Objective: To make a prognostic effect analysis of molecular subtype on young breast cancer patients.

Methods: Totally 187 cases of young breast cancer patients less than 40 years old treated in Obstetrics and Gynecology Hospital of Fudan University between June 2005 and June 2011 were included in our study. We described their clinical-pathological characteristics, disease-free survival (DFS) rate, and overall survival (OS) rate after a median follow-up period of 61 months. The factors associated with prognosis were also evaluated by univariate and multivariate analyses.

Results: All patients were premenopausal, with an average age of 35.36±3.88 years old. The mean tumor size was 2.43±1.53 cm. Eighty-one cases had lymph node metastasis (43.3%), 126 cases had lymphovascular invasion (67.4%), and 125 cases had histological grade III (66.8%) disease. Twenty-seven cases (14.4%) were Luminal A subtype, 99 cases (52.9%) were Luminal B subtype, 29 cases (15.5%) were human epidermal growth factor receptor 2 (HER-2) overexpression subtype, while 32 cases (17.1%) were triple negative breast cancer (TNBC) subtype according to 2013 St Gallen expert consensus. One hundred and thirty-five cases underwent mastectomy whereas 52 cases had breast-conserving surgery. One hundred and seventy-eight cases underwent adjuvant or neoadjuvant chemotherapy. Recurrence or metastasis occurred in 29 cases, 13 of which died. The 5-year DFS and OS rates were 84% and 92%. Multivariate analysis showed that nodal status (P=0.041) and molecular subtype (P=0.037) were both independent prognostic factors of DFS, while nodal status (P=0.037) and TNBC subtype (P=0.048) were both independent prognostic factors of OS.

Conclusions: Molecular subtype is an independent prognostic factor of young breast cancer patients. TNBC has a high risk of relapse and death.

Keywords: Molecular subtype; young breast cancer; prognosis

Introduction

Currently, breast cancer is the most common cancer in Chinese women. This trend is also observed in many other countries. And 12.2% of newly diagnosed breast cancers and 9.6% of deaths due to breast cancer worldwide are from cancer patients in China (1). In the United States, women younger than 40 years old account for 6.6% of breast cancer cases (2). According to International Agency for Research on Cancer, breast cancer cases in women less than 40 years old accounted for 12.56% of all breast cancers in China in 2008, much higher than the proportion in western countries (3). It is commonly recognized that young breast cancer patients are likely to have higher degree of tumor malignancy, higher rate of relapse within an early time period, and worse prognosis (4-6). It is of great clinical importance and social value to investigate biological indicators for breast cancer prognosis, especially for young patients in China. The molecular subtypes of breast cancer were introduced in 2011 (7). Breast cancer of different molecular subtypes has different biological behavior, suggesting that molecular subtype has important value in

comprehensive evaluation of prognosis. There is relatively little literature in China focusing on the prognostic effect of molecular subtypes on young breast cancer patients. This study therefore performed a retrospective analysis of 187 breast cancer patients less than 40 years old treated in Obstetrics and Gynecology Hospital of Fudan University between June 2005 and June 2011.

Patients and methods

Patients

A retrospective study was conducted, in which breast cancer patients less than 40 years old treated in Obstetrics and Gynecology Hospital of Fudan University between June 2005 and June 2011 were enrolled. Inclusion criteria were: (I) pathologic type was breast invasive ductal carcinoma; (II) no evidence of distant metastasis such as bone, liver, lung, brain and so on; (III) underwent mastectomy or breast conserving surgery (BCT); (IV) estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2) and Ki67 were evaluated by immunohistochemistry staining. HER-2(3+) was defined as HER-2 overexpression, HER-2(–) or HER-2(+) was defined as HER-2 negative. Fluorescence *in situ* hybridization (FISH) was needed in cases of HER-2(2+). According to the 2013 St Gallen expert consensus (8), 4 molecular subtypes are defined as: (i) Luminal A, all of: ER and PR positive, HER-2 negative, Ki-67 level <14%; (ii) Luminal B, ER positive, HER-2 negative, and at least one of: Ki-67 >14%, PR negative; or ER positive, HER-2 overexpression, any Ki-67, any PR; (iii) HER-2, HER-2 overexpression, ER and PR negative; and (iv) triple negative breast cancer (TNBC), ER and PR negative, HER-2 negative; (V) intact follow-up records in the hospital. Altogether 187 patients were enrolled in this study and 2 patients were excluded due to lost to follow-up. The 187 patients were then classified into the 4 molecular subtypes retrospectively according to the 2013 St Gallen expert consensus.

Follow-up

The follow-up duration was calculated from the date of diagnosis until the date of death or last contact. Disease-free survival (DFS) was the time between diagnosis and confirmation of disease relapse. Overall survival (OS) was the time between diagnosis and death as a result of recurrence events. The follow-up deadline was June 2014.

Statistical analysis

In this study, the clinical-pathological characteristics were analyzed according to molecular subtypes, such as age, tumor size, histological grade, lymph node status, lymphovascular invasion, TMN stage, surgery type, chemotherapy, radiation therapy, endocrine therapy, etc. The Student's t test and χ^2 test (Pearson statistic) were used to determine the differences in clinical-pathological characteristics between different molecular subtypes of patients. The 5-year DFS and OS were analyzed. Factors such as tumor size (T≤2 cm, T>2 cm), lymph node status, histological grade, lymphovascular invasion, TMN stage, surgery type, chemotherapy, radiation therapy and molecular subtype were taken into univariate analysis to show the association with DFS and OS. Survival estimates were computed using the Kaplan-Meier method and differences between survival times were assessed by means of the Log rank test. Factors with statistical significance in univariate analysis were taken into multivariate analysis to show the independent prognostic factors of DFS and OS. Multivariate analyses were carried out using Cox's proportional hazards model. All statistical analyses were carried out using the SPSS (version 19.0) software package (SPSS Inc., Chicago, IL, USA). P<0.05 was considered statistically significant.

Results

Clinical-pathological characteristics of young breast cancer patients

A total of 187 young breast cancer patients were premenopausal with an average age of 35.36±3.88 years old. The mean tumor size was 2.43±1.53 cm; 81 cases had lymph node metastasis (43.3%), 126 cases had lymphovascular invasion (67.4%), and 125 cases had histological grade III (66.8%) disease. Of the 187 cases, 135 underwent mastectomy whereas 52 breast-conserving surgery.

These 187 cases were retrospectively divided into 4 molecular subtypes according to the 2013 St Gallen expert consensus: 27 cases in Luminal A subtype (14.4%); 99 cases in Luminal B subtype (52.9%); 29 cases in HER-2 subtype (15.5%); and 32 cases in TNBC subtype (17.1%). Clinical-pathological characteristics such as age, histological grade, TMN stage, lymphovascular invasion, surgery type or radiation therapy, did not display a difference among the 4 molecular subtypes in this study (*Table 1*).

Nine cases did not receive chemotherapy (4 cases in

Table 1 Clinical-pathological characteristics of young breast cancer patients according to molecular subtypes

Characteristics	Case No.				P
	TNBC (N=32)	HER-2 (N=29)	Luminal A (N=27)	Luminal B (N=99)	
Age (year)	34.66±4.84	35.48±3.80	36.22±3.34	35.32±3.82	0.476
Histological grade					0.612
II	10	9	12	31	
III	22	20	15	68	
T					0.078
T1	5	10	14	37	
T2	24	14	10	48	
T3	3	5	3	14	
N					0.365
N0	19	14	20	53	
N1	7	11	7	27	
N2	3	3	0	9	
N3	3	1	0	10	
Lymphovascular invasion					0.291
Yes	23	18	22	63	
No	9	11	5	36	
TMN stage					0.290
I	4	6	10	18	
II	22	19	15	62	
III	6	4	2	19	
ER					<0.001
Positive	0	0	27	55	
Negative	32	29	0	44	
PR					<0.001
Positive	0	0	27	39	
Negative	32	29	0	60	
HER-2					<0.001
(−)(+)	32	0	27	61	
(+++) or FISH(+)	0	29	0	38	
Surgery					0.925
Mastectomy	24	22	19	70	
BCT	8	7	8	29	
Chemotherapy					0.029
Yes	32	29	23	94	
No	0	0	4	5	
Radiation therapy					0.145
Yes	7	7	8	40	
No	25	22	19	59	
Endocrine therapy					<0.001
Yes	0	0	27	97	
No	32	29	0	2	

TNBC, triple negative breast cancer; HER-2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; FISH, fluorescence *in situ* hybridization; BCT, breast conserving surgery.

Table 2 Relapses and deaths in 187 young breast cancer patients

Prognosis	n (%)			
	TNBC (N=32)	HER-2 (N=29)	Luminal A (N=27)	Luminal B (N=99)
Relapses	8 (25.0%)	3 (10.3%)	1 (3.7%)	17 (17.2%)
Deaths	5 (15.6%)	2 (6.9%)	0	6 (6.1%)

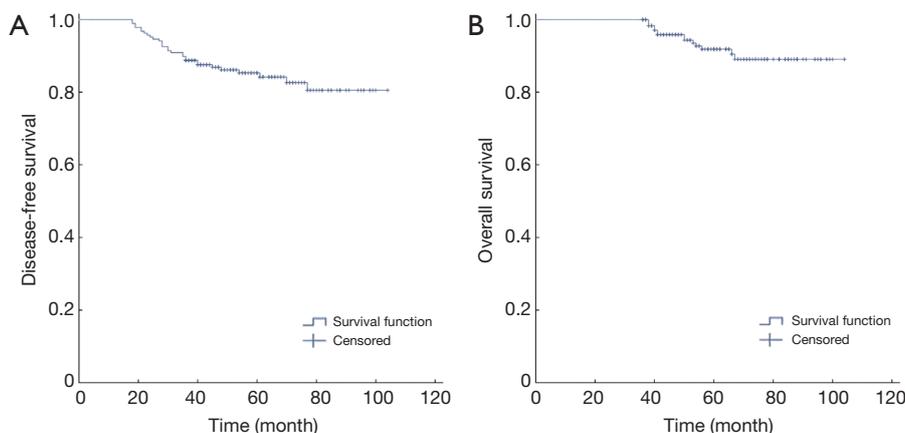TNBC, triple negative breast cancer; HER-2, human epidermal growth factor receptor 2.

Figure 1 Survival curves of young breast cancer. (A) Disease-free survival (DFS); (B) overall survival (OS).

Luminal A and 5 cases in Luminal B). These cases were all in TMN stage I with a tumor size less than 2 cm, negative lymph nodes, histological grade II, high ER level, HER-2 negativity and negative lymphovascular invasion. The other cases received adjuvant chemotherapy or neoadjuvant chemotherapy. Cases with 4 or more lymph node metastases, a tumor size over 5 cm, or receiving BCT routinely underwent adjuvant radiation therapy after surgery. Cases that were ER or PR positive received endocrine therapy. Two cases ceased endocrine therapy because of intolerance of adverse effect of the drugs. Cases with HER-2 overexpression were strongly recommended trastuzumab. Eighteen cases in HER-2 subtype received trastuzumab, while 10 cases in Luminal B subtype, in which 38 cases had HER-2 overexpression, received trastuzumab.

Survival analysis of young breast cancer patients and prognostic factors of survival

Within a median follow-up period of 61 months (36-104 months), tumor relapse occurred in 29 cases, among which 13 cases died (*Table 2*). The 5-year DFS was 84% and the 5-year OS was 92% (*Figure 1*).

At univariate analysis, lymph node status (P=0.038) and molecular subtype (P=0.044) were significantly associated with DFS (*Figure 2A,B*). When the molecular subtypes were divided into TNBC and non-TNBC, the association was still significant between molecular subtype and DFS (P=0.038) (*Figure 2C*). Lymph node status was significantly associated with OS (P=0.015), whereas molecular subtype was not statistically significantly associated with OS (P=0.060) (*Figure 3A,B*). When the molecular subtypes were divided into TNBC and non-TNBC, the molecular subtype was statistically significantly associated with OS (P=0.023) (*Figure 3C*).

At multivariate analysis, lymph node status (P=0.041) and molecular subtype (P=0.037) were both independent prognostic factors for DFS (*Table 3*). When molecular subtypes were divided into TNBC and non-TNBC, the lymph node status (P=0.037) and TNBC subtype (P=0.048) were both independent prognostic factors for OS (*Table 4*).

Discussion

Whether age is an independent risk factor for breast cancer survival is controversial. Han *et al.* supported that young
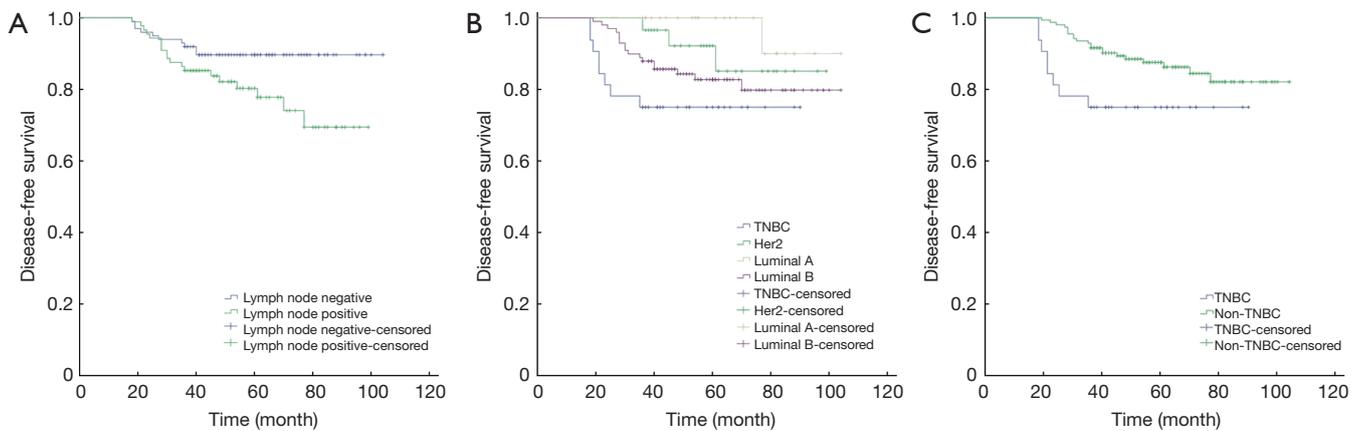
Figure 2 DFS curves of young breast cancer according to lymph node status and molecular subtypes. (A) According to lymph node status; (B) according to molecular subtypes; (C) according to molecular subtypes of TNBC and non-TNBC. DFS, disease-free survival; TNBC, triple negative breast cancer.
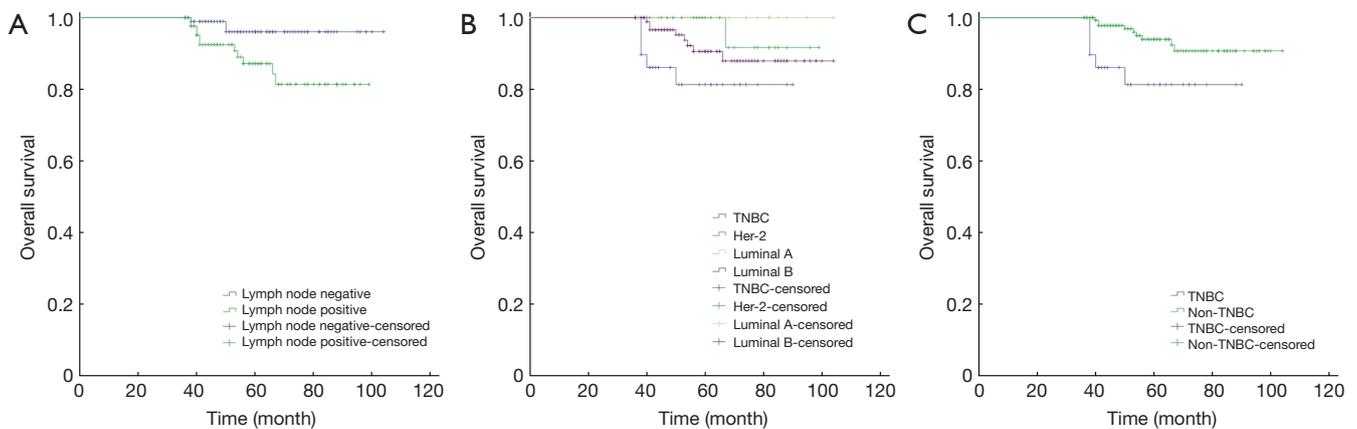

Figure 3 OS curves of young breast cancer according to lymph node status and molecular subtypes. (A) According to lymph node status; (B) according to molecular subtypes; (C) according to molecular subtypes of TNBC and non-TNBC. OS, overall survival; TNBC, triple negative breast cancer.

Table 3 Multivariate Cox's analysis of DFS of young breast cancer

Item	HR	95% CI	P
Lymph node status (positive:negative)	1.954	1.004-3.804	0.041
Molecular subtype			0.037
HER-2:TNBC	0.284	0.105-0.963	
Luminal A:TNBC	0.102	0.013-0.795	
Luminal B:TNBC	0.549	0.259-1.164	

DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; HER-2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

Table 4 Multivariate Cox's analysis of OS of young breast cancer

Item	HR	95% CI	P
Lymph node status (positive:negative)	2.256	1.048-4.855	0.037
Molecular subtype (non-TNBC:TNBC)	0.439	0.194-0.993	0.048

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; TNBC, triple negative breast cancer.

age (<35 years old) is an independent risk factor for relapse in operable breast cancer patients through multivariate analysis of OS (9). However, other scholars identified that age was not significantly related to mortality from breast cancer when accounting for all prognostic variables (10). Although there is no perspective study supporting young age as an independent prognostic factor, it can be regarded as a risk predictor for survival. Age should be considered, in association with other pathological and biological factors, in the treatment of breast cancer, so that young breast cancer patients can receive more effective therapeutic regimens.

Molecular subtypes of breast cancer were introduced to reflect the biology of tumors and marked differences in patient prognosis (11,12). The distribution of molecular subtypes is somewhat different among young patients and their older counterparts. Compared with older women, young women had higher proportions of hormone receptor (HR)(+)/HER-2(+), triple negative and HR(–)/HER-2(+) breast cancer (13). Furthermore, there may be differences in prognosis even for the same subtype. For example, Luminal B tumors among young women, when compared with the older group, demonstrated more aggressive features (14) and had worse outcomes (15). An Italian, institution-based study found worse survival in women <35 years of age compared with older women (35 to 50 years of age) for triple-negative, Luminal B, and HER-2-positive cancer (15). Recently, molecular subtypes showed a prognostic association with outcome in patients <65 years of age with regards to the relapse free period (RFP) (P=0.01) and relative survival (RS) (P<0.001). However, no statistically significant prognostic effect was found for molecular subtypes in patients >65 years of age (16). Therefore, it is worthwhile to conduct a study to evaluate the prognostic effect of molecular subtypes in young breast cancer patients (<40 years of age).

Multiple studies have indicated that young breast cancer patients are more likely to have a higher proportion of histological grade III (62-80%), negative ER and PR (33-80%), HER-2 overexpression (29-44%) (17,18), TNBC subtype (19,20), lymph node invasion and lymphovascular invasion (6,9,10,21,22). Our study was in agreement with the literature.

In our study, histological grade and tumor size (over 2 cm) were not associated with survival for young breast cancer patients. In the cases in our cohort, only 25 cases had a tumor mass over 5 cm and most cases were in the T1 and T2 stages with a mean tumor size of 2.83±1.53 cm. There was no significant difference in tumor size stage among the molecular subtypes in our study. Among 66 cases in the T1 stage, 23 were presented with positive lymph node status and 8 events of tumor relapse occurred. Shen indicated that in cases with 1-3 and 4-6 lymph nodes involved, the survival rate was not different when the tumor size was less than 5 cm, but there was a significant difference when the tumor size was larger than 5 cm (23). In addition, Wo *et al*. also found that very small tumors with 4 positive lymph nodes may predict for higher breast cancer specific mortality compared with larger tumors. In cases with extensive node-positive disease, very small tumor sizes may be a surrogate for biologically aggressive disease (24). Therefore, tumor size over 2 cm was not a prognostic factor in our study.

Our study also showed that BCT was not a risk factor for tumor relapse. Cao *et al*. examined 15-year outcomes among 616 women younger than 40 years old treated with BCT plus whole-breast radiation therapy, compared with 349 patients treated with modified radical mastectomy (MRM). The OS (74.2% *vs*. 73.0%, P=0.75), local relapse-free survival (85.4% *vs*. 86.5%, P=0.95) and distant relapse-free survival (74.4% *vs*. 71.6%, P=0.40) were similar between the BCT and MRM cohorts (25). There is another study showing a moderately higher local recurrence rate in young breast cancer patients compared with older patients after 5-10 year follow-up, but similar distant relapse-free survival rate and OS rate as well (26). Taken into account the psychological trauma of young patients as the result of mastectomy, we recommend BCT plus radiation therapy and long-term follow-up in appropriate cases.

In our study, 178 cases (95.2%) received chemotherapy. Therefore, chemotherapy status could not be included as a prognostic factor through statistical analysis because of

the high rate of chemotherapy in our study. Agnese *et al.* supported chemotherapy in younger women even with node-negative tumors less than 1 cm in diameter (27). Clive *et al.* indicated that chemotherapy was increasingly being considered appropriate for all women under the age of 35 years old, regardless of other risk factors (28). DFS was obviously low in young patients without adjuvant chemotherapy (29). Kroman *et al.* found that young women with low risk disease who did not receive adjuvant chemotherapy had a significantly increased risk of dying. Risk increased with decreasing age at diagnosis [for patients <35 years: odds ratio (OR)=2.18, 95% confidence interval (95% CI): 1.64 to 2.89] even when women were grouped according to the presence of node negative disease and by tumor size (30). A meta-analysis by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) indicated that the risk reductions through chemotherapy regimens were more apparent in young patients compared with older patients (31). In the 2013 St Gallen expert consensus, chemotherapy is needed in the TNBC subtype, HER-2 subtype, most cases of Luminal B subtype, and in cases of Luminal A subtype with high risk factors (such as grade III disease, involvement of 4 or more lymph nodes, etc.) (8). From the retrospective analysis, 9 cases who did not receive chemotherapy were in the Luminal subtype without high risk factors. Thus, all cases in our study underwent appropriate treatment in view of the current guidelines.

Other research groups have shown that the worse prognosis of young breast cancer patients was associated with a high proportion of ER negativity and HER-2 overexpression, which were strong prognostic factors (32,33). Furthermore, Ki67, which is closely related with cell proliferation, was also considered as an independent prognostic factor (34). The introduction of molecular subtypes in 2011, which integrates factors such as ER, PR, HER-2 and Ki67 as a whole, provided a more comprehensive prediction of breast cancer prognosis. Recent studies also indicated that lymph node metastasis, ER negativity and HER-2 overexpression were not all causes of worse prognosis in young patients. HER-2 and ER status were not independent prognostic factors. It was suggested that ER status was an important indicator for endocrine therapy rather than an independent prognostic factor and HER-2 overexpression was of no prognostic value in node negative cases (35).

Our study indicated that lymph node status and molecular subtypes were both prognostic factors of DFS and OS. In other studies, a statistically significant association (P=0.02) was found between molecular subtypes and age, where HER-2 and TNBC subtypes were more often found in young patients. Molecular subtypes showed a prognostic association with outcome in young patients with regards to relapse-free survival (P=0.01) and relative survival (P<0.001) (16). In the multivariate analysis, triple-negative status was the only independent prognostic factor which affected the DFS adversely [hazard ratio (HR): 1.48, 95% CI: 0.66-0.82, P=0.027] (36). In our study, relapse occurred in 8 cases in TNBC, among whom, 4 cases were node negative (50%). It was pointed out that TNBC had a worse prognosis without a very high rate of lymph node metastasis (37). Patients with TNBC are not more likely to have involved nodes than those with non-TNBC (38). Compared with HR(+)/HER-2(−) tumors as the reference group, TNBC subtype was associated with a lower risk of node positivity (OR=0.88, 95% CI: 0.80-0.97; P<0.001) (39). High risk of relapse still exists in young TNBC patients even with negative lymph nodes. It was reported that the 5-year OS in young TNBC patients with node negativity was as low as 80.5% (40). In patients with TNBC, once there was evidence of lymph node metastasis, the prognosis may not be affected by the number of positive lymph nodes (41). The accurate prediction of prognosis can be made using the integration of lymph node status and molecular subtype.

Our study showed the lowest DFS and OS in TNBC, followed by Luminal B subtype and HER-2 subtype. Among 29 cases which relapsed, 8 cases were in TNBC (27.6% of all relapses), which accounted for 25% of all cases in the TNBC subtype. Among the 13 cases that died, 5 cases were in TNBC (38.5% of all deaths), which accounted for 15.6% of all cases in the TNBC subtype. Eighteen cases in the HER-2 subtype (62.1%) received trastuzumab, which helped to improve their prognosis (42). While in the Luminal B subtype, the trastuzumab application rate was 26.3%, which maybe had a negative prognostic effect. High hormone levels and relatively insufficient ovarian suppression may contribute to a high relapse rate in young breast cancer patients (43). In standardized and personal treatments, more attention should be paid not only to the TNBC subtype, but also to the Luminal B subtype which accounts for the majority of young breast cancer patients (44).

There were also some limitations to our study, such as relatively small number of cases and selection bias, which was unavoidable because this was a retrospective cohort study. Most cases were in the early stages, of which TMN I and II stages accounted for the majority, which may

attribute to the improvement of diagnosis and treatment, and more focus on breast disease. With more attention drawn towards the molecular subtypes in breast cancer, young patients will receive more appropriate personal treatment according to their predicted prognosis. Further investigation is warranted in the TNBC subtype which has a relatively worse prognosis, and in the Luminal B subtype as well, which currently lacks sufficient attention.

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Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

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