SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 17: 1505-1516, 2019

Use of clinical nomograms for predicting survival outcomes in young women with breast cancer

HUI LIN[1*], FAN ZHANG[2*], LUANHONG WANG[3] and DE ZENG[1]

[1]Department of Breast Medical Oncology; [2]Guangdong Provincial Key Laboratory for Breast Cancer Diagnosis and Treatment; [3]Department of Gynecology, Cancer Hospital of Shantou University Medical College, Shantou, Guangdong 515041, P.R. China

Received December 4, 2017; Accepted October 12, 2018

DOI: 10.3892/ol.2018.9772

Abstract. Early-onset breast cancer (BC) has been recognized to be more aggressive compared with its later counterparts. Survival models of BC in young patients have rarely been reported in previous studies. The current study aimed to establish and validate prediction models with clinicopathological variables for visceral metastasis-free survival (VFS), disease-free-survival (DFS) and overall survival (OS) time in young patients with BC. Clinicopathological data were obtained for 351 patients with primary breast tumors who were ≤40 years old. Univariate and multivariate analyses were performed and nomograms were established to screen and illustrate the prognostic factors. Risk scores were calculated based on coefficients from the Cox regression analysis. Internal validation of the prediction models was conducted by predicting the prognosis of cases randomly sampled from the cohort used in the current study. Multivariate analysis demonstrated that N stage (P=0.004), molecular subtype (P=0.007) and age (P=0.005) were significant independent prognostic factors for VFS. Similarly, N stage (P=0.002) and molecular subtype (P=0.001) were significantly associated with DFS. In addition, N stage (P=0.006), molecular subtype (P=0.006) and the presence of an initially inoperable tumor (P=0.005) were significant independent prognostic factors for OS. According to the Cox regression analysis, nomograms were generated to illustrate the effect of independent prognostic factors on VFS, DFS and OS. Risk scores were calculated and internal validation demonstrated the reliability of the prediction models. In conclusion, N stage and molecular subtype were identified as predictors for VFS, DFS and OS in early-onset BC. Furthermore, an age of <35 years at diagnosis was revealed to be unfavorable for VFS and the presence of an initially inoperable tumor was identified to reduce OS time.

Correspondence to: Dr Hui Lin, Department of Breast Medical Oncology, Cancer Hospital of Shantou University Medical College, 7 Raoping Road, Shantou, Guangdong 515041, P.R. China
E-mail: hlin3@stu.edu.cn

*Contributed equally

Abbreviations: BC, breast cancer; VFS, visceral metastasis-free survival; DFS, disease-free survival; OS, overall survival; ER, estrogen receptor; PR, progesterone receptor; HBV, hepatitis B virus; IHC, immunohistochemistry

Key words: young patient with breast cancer, survival model, nomogram, visceral metastasis-free survival, disease-free survival, overall survival

Introduction

Breast cancer (BC) is the leading cause of cancer-associated mortality among women worldwide (1). In the past decade, the mortality rate has decreased in the majority of high-income countries; however, the incidence and mortality rates have increased in China (1). This may be due to a number of factors, including the one-child policy, lower cancer screening rates and delays in cancer diagnosis (2). In addition, the median age at diagnosis of BC is 48-50 years in China and 62.9% of patients are premenopausal at that time (2).

BC in younger women has been recognized to be more aggressive and exhibits a worse prognosis compared with BC in older women (3,4). Previous studies have identified that, compared with older patients, younger women with BC present with a larger tumor size, a higher incidence of lymph node involvement (4,5) and an increased 5-year risk of developing metastasis (3,6). Compared with older women, young women exhibit higher proportions of hormone receptor (HR)$^+$/human epidermal growth factor receptor 2 (HER-2)$^+$, HR$^-$/HER2$^+$ and triple-negative BC (5,7). Diverse molecular subtypes usually have distinct disease-free survival (DFS) and overall survival (OS) rates (6,8), and age has been identified to serve different roles (9,10). Clinicians use certain risk scores in clinical practice, including the commonly used St Gallen risk factor grading system (11). In this grading system, age is one of the most valuable factors, which suggests that similar to estrogen receptor (ER) status and lymph node status, age is fundamental in predicting BC prognosis. Previous studies have predominantly focused on the clinicopathological features of BC in young patients (3,12). However, to the best of our knowledge, a survival model remains to be established. The current study investigated a number of factors, including T stage, N stage, pathological type, grade, surgical type, neoadjuvant chemotherapy, age and molecular subtype, for predicting survival in

young patients with BC. The study aimed to assess an array of clinicopathological variables that are potentially associated with visceral metastasis-free survival (VFS), DFS and OS. In addition, the ultimate aim of the study was to establish and validate prediction models for survival outcomes in young patients with BC.

Patients and methods

Definition of a young patient with BC. The definition of a young patient with BC varies among previous studies. Previously, the upper age limit has ranged from 35 (13) to 40 years (14,15). The current study defined young BC as patients ≤40 years old at preliminary diagnosis.

Study population. A total of 351 females with primary BC who were diagnosed at ≤40 years old and treated at the Cancer Hospital of Shantou University Medical College (Guangdong, China) between April 2009 and May 2014 were included in the current study. The inclusion criteria were: i) female; ii) breast cancer confirmed by pathological diagnosis; and iii) age ≤40 years old. Patients with distant metastasis at primary diagnosis and patients with a follow-up time <6 months were excluded. The mean age of the patients was 35.74 years with a range of 19 to 40 years. Every patient had undergone mammographic and/or ultrasound radiological imaging, a chest radiograph or computed tomography scan of the chest, Doppler ultrasound examination or a computed tomography scan of the abdomen, a complete blood count test and blood biochemistry assays to evaluate the primary tumor stage and the appropriate treatment. Bone scans and brain magnetic resonance imaging were performed if patients experienced bone pain, central nervous symptoms or exhibited a locally advanced stage of BC. Patients with primary resectable tumors received a mastectomy or breast-conserving surgery with axillary lymph node dissection or sentinel lymph node biopsy. A core needle biopsy was performed in a standardized manner when the surgeon identified that a tumor was inoperable. Neoadjuvant chemotherapy was administered to patients with initially inoperable tumors, the majority of which were stages T3/T4 and/or N2/N3 according to the 7th edition of the American Joint Committee on Cancer staging system (16), to increase the possibility of radical surgeries later on. The requirement of adjuvant chemotherapy and the protocol of the chemotherapy treatment were guided by the St. Gallen BC guidelines (11).

Clinical and pathological data were collected from patient records. Histopathological features of surgical resection specimens included tumor type and size, histological grade, evidence of lymphovascular invasion and axillary nodal status. ER, progesterone receptor (PR), HER-2, Ki-67 and other markers were stained in the majority of the biopsy and resection specimens. Adjuvant radiotherapy, chemotherapy, endocrine treatment and targeted treatment were recorded. In addition, other basic information, including age of menarche, fertility status, hepatitis B virus (HBV) infection and family history were recorded. Follow-up information was obtained from patient records. The median follow-up time was 38.3 months (range, 6.0-106.6 months).

Written informed consent was obtained from all participants for the use of clinicopathological data. The current study was approved by the Ethics Committee of the Cancer Hospital of Shantou University Medical College.

Classification of survival and molecular subtypes. VFS was defined as the time from radical surgery to visceral metastasis, excluding local relapse and metastasis of the lymph nodes and bones. DFS was defined as the time from radical surgery to disease relapse or metastasis, including visceral metastasis. OS was defined as the time from diagnosis to mortality from any cause. Molecular subtypes were differentiated according to the status of ER, PR and HER-2, as determined by immunohistochemistry (IHC). As the cut-off value of Ki-67 has not previously been determined (17) and since testing for Ki-67 was not routinely performed in the study period, the current study did not use Ki-67 for the classification of molecular subtypes. The molecular subtypes were defined as follows: The luminal A subtype, which was HER-2$^-$, ER$^+$ and/or PR$^+$; the luminal B subtype, which was HER-2$^+$, ER$^+$ and/or PR$^+$; the HER-2$^+$ subtype, which was HER-2$^+$, ER$^-$ and PR$^-$; and the triple-negative subtype, which was HER-2, ER and PR. HER-2 positivity was defined as HER-2 gene amplification in a fluorescence *in situ* hybridization test or HER-2 protein stained as '+++' in IHC, as described previously (18).

Statistical analysis. All statistical analyses were performed using SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA) and R software (version 3.3.0; www.r-project.org). The univariate analysis for assessing the prognostic factors was performed using the Kaplan-Meier method with a log-rank test. Variables associated with survival ($P<0.05$) were selected for multivariate Cox regression analysis using forward stepwise selection. Nomograms were then generated to illustrate the effect of the prognostic factors on DFS, VFS and OS. Risk scores were created based on Cox regression coefficients. Each patient was assigned a risk score that was a linear combination of the values of the independent prognostic factors weighted by their respective Cox regression coefficients (19). Internal validation of the prediction models was performed by evaluating the accuracy of the risk score on the prognosis of 200, 250 and 300 patients who were randomly selected from the total 351 patients. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Univariate survival analysis for predicting DFS, VFS and OS in young patients with BC. To preliminarily determine the potential prognostic factors, univariate survival analysis was performed for VFS, DFS and OS. The median follow-up time was 38.3 months and the median values for VFS, DFS and OS were 38.0, 33.5 and 38.2 months, respectively. The variables included in the analysis were age, T stage, N stage, M stage, site of involvement, pathological type, differentiation grade, molecular subtype, surgical type, neoadjuvant chemotherapy, adjuvant radiation, age of menarche, fertility status, HBV infection and family history.

The 1-, 3- and 5-year VFS rates were 94.5, 87.6 and 80.6%, respectively. The 1-, 3- and 5-year DFS rates were 89.8, 76.2 and 64.6%, respectively. The 1-, 3- and 5-year OS rates were 98.2, 87.4 and 73.3%, respectively. Survival rates for different

Table I. Clinicopathological characteristics of patients and the associated 1-, 3- and 5-year VFS rates.

Characteristic	Cases, n (%)	VFS, %			P-value
		1-year	3-year	5-year	
Age, years					0.005
<35	108 (30.8)	93.4	82.8	67.0	
≥35	243 (69.2)	95.0	89.6	85.3	
T stage					0.014
Tis	1 (0.3)				
T1	64 (18.2)	96.4	89.0	81.8	
T2	163 (46.4)				
T3	52 (14.8)	88.2	79.5	74.2	
T4	25 (7.1)				
Unknown	46 (13.1)				
N stage					0.004
N0	144 (41.0)	97.2	93.7	92.2	
N1	80 (22.8)	96.2	87.1	74.2	
N2	57 (16.2)	94.6	88.3	71.9	
N3	56 (16.0)	83.5	73.3	73.3	
Unknown	14 (4.0)				
M stage					0.544
M0	339 (96.6)	94.6	87.5	80.4	
M1[a]	6 (1.7)	83.3	83.3	0.0	
Unknown	6 (1.7)				
Site of involvement					0.596
Left	177 (50.4)	94.8	89.4	81.2	
Right	166 (47.3)	93.8	86.2	80.8	
Bilateral	8 (2.3)	100.0	75.0	75.0	
Pathological type					0.029
IDC	290 (82.6)	93.3	85.3	76.7	
ILC	11 (3.1)	100.0	100.0	100.0	
DCIS	22 (6.3)	100.0	100.0	100.0	
Other	27 (7.7)	100.0	96.0	96.0	
Unknown	1 (0.3)				
Grade					0.063
I	15 (4.3)	100.0	100.0	100.0	
II	103 (29.3)	92.0	88.5	86.2	
III	96 (27.4)	93.7	78.2	70.6	
Unknown	137 (39.0)				
Molecular subtype					0.007
Luminal A	161 (45.9)	98.1	90.9	85.9	
Luminal B	40 (11.4)	97.4	92.0	78.7	
HER-2$^+$	47 (13.4)	80.6	70.8	66.6	
Triple-negative	65 (18.5)	90.7	83.0	75.4	
Unknown	38 (10.8)				
Surgical type					0.120
Modified radical mastectomy	276 (78.6)	93.0	86.3	78.2	
Breast-conserving surgery	58 (16.5)	100.0	92.6	92.6	
Mastectomy and SLNB	12 (3.4)	100.0	100.0	100.0	
Simple resection[b]	5 (1.4)	100.0	75.0	-[c]	
Neoadjuvant chemotherapy					0.020
Yes	46 (13.1)	86.9	76.5	69.6	
No	305 (86.9)	95.6	89.2	82.1	

Table I. Continued.

Characteristic	Cases, n (%)	VFS, %			P-value
		1-year	3-year	5-year	
Adjuvant radiation					0.399
Yes	190 (54.1)	92.9	84.5	80.3	
No	161 (45.9)	96.3	91.1	81.3	
Age of menarche, years					0.934
≤15	252 (71.8)	95.1	88.3	79.2	
>15	50 (14.2)	94.0	86.6	86.6	
Unknown	49 (14.0)				
Fertility status					0.566
Yes	323 (92.0)	94.3	87.6	80.5	
No	27 (7.7)	96.3	87.4	80.1	
Unknown	1 (0.3)				
HBV infection					0.477
Yes	9 (2.6)	88.9	74.1	74.1	
No	342 (97.4)	94.6	87.9	80.7	
Family history					0.143
BC	8 (2.3)	100.0	100.0	50.0	
Other cancer types	13 (3.7)	100.0	64.1	64.1	
No	330 (94.0)	94.1	88.2	82.2	

[a]Patients with bone metastasis at diagnosis; [b]patients received simple resection in another hospital prior to administration; [c]censored data. VFS, visceral metastasis-free survival; Tis, tumor in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; HER-2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; BC, breast cancer; HBV, hepatitis B virus.

clinicopathological features were analyzed and tested with Kaplan-Meier analysis and a log-rank test (Tables I-III). This analysis identified that for VFS, N stage (P=0.004), molecular subtype (P=0.007), age (P=0.005), T stage (P=0.014), pathological type (P=0.029) and neoadjuvant chemotherapy (P=0.020) were statistically significant variables. For DFS, N stage (P=0.002) and molecular subtype (P=0.001) were statistically significant. For OS, T stage (P=0.029), N stage (P=0.006), M stage (P=0.002), molecular subtype (P=0.006), surgical type (P<0.001) and neoadjuvant chemotherapy (P=0.005) were statistically significant variables.

Multivariate survival analysis for predicting VFS, DFS and OS in young patients with BC. To further analyze the prognostic factors for VFS, DFS and OS, multivariate survival analysis was performed. Variables revealed as statistically significant by Kaplan-Meier analysis (P<0.05) were selected for Cox regression analysis to identify independent factors. As presented in Table IV, the variables analyzed for VFS were as follows: N stage (P<0.001); molecular subtype (P=0.027); and age (P<0.001). As presented in Table V, the variables analyzed for DFS included: N stage (P=0.004) and molecular subtype (P=0.002). As presented in Table VI, the variables analyzed for OS were as follows: N stage (P=0.029), molecular subtype (P=0.006) and neoadjuvant chemotherapy (P=0.006). Nomograms were created to illustrate the effect of the prognostic factors on VFS, DFS and OS using multivariate Cox regression coefficients (Figs. 1-3).

Risk scores for predicting survival outcomes in young patients with BC. Based on the regression analysis, prediction models for VFS, DFS and OS were generated through the calculations of risk scores, previously established by Shukla *et al* (19). Each patient was assigned a risk score; a linear combination of the values of the independent prognostic factors weighted by their respective Cox regression coefficients. Risk scores for VFS were calculated as follows: Risk score = 1.091 x N stage (N1/N0) + 1.499 x N stage (N2/N0) + 2.163 x N stage (N3/N0) + 0.355 x molecular subtype (luminal B/luminal A) + 1.087 x molecular subtype (HER-2/luminal A) + 1.016 x molecular subtype (triple-negative/luminal A) + 1.319 x age (<35/≥35). Risk scores for DFS were calculated as follows: Risk score = 0.555 x N stage (N1/N0) + 0.831 x N stage (N2/N0) + 1.112 x N stage (N3/N0) + 0.613 x molecular subtype (luminal B/luminal A) + 1.109 x molecular subtype (HER-2/luminal A) + 0.665 x molecular subtype (triple-negative/luminal A). Risk scores for OS were calculated as follows: Risk score = 0.050 x N stage (N1/N0) + 0.636 x N stage (N2/N0) + 1.166 x N stage (N3/N0) - 0.033 x molecular subtype luminal B/luminal A) + 1.033 x molecular subtype (HER-2/luminal A) + 1.182 x molecular subtype (triple-negative/luminal A) + 1.001 x neoadjuvant chemotherapy (yes/no).

Internal validation of the prediction models was conducted by evaluating the effect of the risk score on the prognosis of patients. A total of 200, 250 and 300 cases were randomly selected 10 times from the total 351 cases and univariate Cox

Table II. Clinicopathological characteristics of patients and the associated 1-, 3- and 5-year DFS rates.

Characteristic	Cases, n (%)	DFS, %			P-value
		1-year	3-year	5-year	
Age, years					0.241
<35	108 (30.8)	86.7	74.1	61.1	
≥35	243 (69.2)	91.1	77.2	65.5	
T stage					0.053
Tis	1 (0.3)				
T1	64 (18.2)	91.9	79.2	68.8	
T2	163 (46.4)				
T3	52 (14.8)	83.9	68.7	59.0	
T4	25 (7.1)				
Unknown	46 (13.1)				
N stage					0.002
N0	144 (41.0)	93.0	86.5	79.8	
N1	80 (22.8)	93.6	76.5	60.4	
N2	57 (16.2)	91.0	72.2	46.9	
N3	56 (16.0)	75.3	61.2	61.2	
Unknown	14 (4.0)				
M stage					0.102
M0	339 (96.6)	90.4	76.8	66.1	
M1[a]	6 (1.7)				
Unknown	6 (1.7)				
Site of involvement					0.178
Left	177 (50.4)	90.2	78.2	65.3	
Right	166 (47.3)	89.4	75.4	64.7	
Bilateral	8 (2.3)	87.5	50.0	50.0	
Pathological type					0.078
IDC	290 (82.6)	89.8	73.9	61.0	
ILC	11 (3.1)	100.0	100.0	100.0	
DCIS	22 (6.3)	95.0	95.0	76.0	
Other	27 (7.7)	80.7	76.7	76.7	
Unknown	1 (0.3)				
Grade					0.241
I	15 (4.3)	86.2	79.0	79.0	
II	103 (29.3)	86.1	80.1	72.1	
III	96 (27.4)	88.2	65.2	59.3	
Unknown	137 (39.0)				
Molecular subtype					0.001
Luminal A	161 (45.9)	96.1	81.4	72.0	
Luminal B	40 (11.4)	89.9	76.6	46.6	
HER-2$^+$	47 (13.4)	69.2	55.0	50.8	
Triple-negative	65 (18.5)	86.0	71.4	64.9	
Unknown	38 (10.8)				
Surgical type					0.077
Modified radical mastectomy	276 (78.6)	88.9	74.3	62.1	
Breast-conserving surgery	58 (16.5)	93.0	84.1	77.1	
Mastectomy and SLNB	12 (3.4)	100.0	100.0	100.0	
Simple resection[b]	5 (1.4)	80.0	53.3	-[c]	
Neoadjuvant chemotherapy					0.051
Yes	46 (13.1)	81.7	63.0	56.7	
No	305 (86.9)	90.9	78.2	65.7	

Table II. Continued.

Characteristic	Cases, n (%)	DFS, %			P-value
		1-year	3-year	5-year	
Adjuvant radiation					0.081
Yes	190 (54.1)	91.8	77.6	71.6	
No	161 (45.9)	87.4	74.5	57.1	
Age of menarche, years					0.494
≤15	252 (71.8)	91.0	78.1	63.6	
>15	50 (14.2)	83.7	71.5	67.8	
Unknown	49 (14.0)				
Fertility status					0.966
Yes	323 (92.0)	89.2	76.1	63.8	
No	27 (7.7)	96.3	76.0	69.1	
Unknown	1 (0.3)				
HBV infection					0.584
Yes	9 (2.6)	88.9	74.1	49.4	
No	342 (97.4)	89.8	76.3	65.1	
Family history					0.139
BC	8 (2.3)	100.0	85.7	57.1	
Other cancer types	13 (3.7)	83.3	53.3	26.7	
No	330 (94.0)	89.7	76.9	66.3	

[a]Patients with bone metastasis at diagnosis; [b]patients received simple resection in another hospital prior to administration; [c]censored data. DFS, disease-free survival; Tis, tumor in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; HER-2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; BC, breast cancer; HBV, hepatitis B virus.

Table III. Clinicopathological characteristics of patients and the associated 1-, 3- and 5-year OS rates.

Characteristic	Cases, n (%)	OS, %			P-value
		1-year	3-year	5-year	
Age, years					0.387
<35	108 (30.8)	96.2	84.6	71.5	
≥35	243 (69.2)	99.6	88.4	75.9	
T stage					0.029
Tis	1 (0.3)				
T1	64 (18.2)	99.5	90.5	80.2	
T2	163 (46.4)				
T3	52 (14.8)	94.7	80.8	73.7	
T4	25 (7.1)				
Unknown	46 (13.1)				
N stage					0.006
N0	144 (41.0)	98.6	93.2	84.2	
N1	80 (22.8)	98.7	89.7	81.5	
N2	57 (16.2)	98.2	85.9	64.6	
N3	56 (16.0)	98.1	78.2	64.9	
Unknown	14 (4.0)				
M stage					0.002
M0	339 (96.6)	98.5	88.9	75.9	
M1[a]	6 (1.7)	100.0	50.0	-[c]	
Unknown	6 (1.7)				

Table III. Continued.

Characteristic	Cases, n (%)	OS, %			P-value
		1-year	3-year	5-year	
Site of involvement					0.439
Left	177 (50.4)	98.2	90.6	77.3	
Right	166 (47.3)	98.8	83.9	71.4	
Bilateral	8 (2.3)	100.0	75.0	75.0	
Pathological type					0.289
IDC	290 (82.6)	98.2	86.2	71.8	
ILC	11 (3.1)	100.0	100.0	75.0	
DCIS	22 (6.3)	100.0	95.0	95.0	
Other	27 (7.7)	100.0	86.6	86.6	
Unknown	1 (0.3)				
Grade					0.103
I	15 (4.3)	100.0	100.0	100.0	
II	103 (29.3)	98.0	86.3	82.3	
III	96 (27.4)	97.9	81.3	69.1	
Unknown	137 (39.0)				
Molecular subtype					0.006
Luminal A	161 (45.9)	100.0	90.8	78.9	
Luminal B	40 (11.4)	97.4	94.9	81.9	
HER-2$^+$	47 (13.4)	97.8	71.8	57.1	
Triple-negative	65 (18.5)	95.2	81.5	65.3	
Unknown	38 (10.8)				
Surgical type					<0.001
Modified radical mastectomy	276 (78.6)	98.1	86.8	72.9	
Breast-conserving surgery	58 (16.5)	100.0	95.3	90.8	
Mastectomy and SLNB	12 (3.4)	100.0	88.9	-[c]	
Simple resection[b]	5 (1.4)	100.0	0.0	0.0	
Neoadjuvant chemotherapy					0.005
Yes	46 (13.1)	93.3	70.9	63.0	
No	305 (86.9)	99.3	89.8	76.3	
Adjuvant radiation					0.559
Yes	190 (54.1)	98.9	90.0	74.9	
No	161 (45.9)	98.1	84.2	74.3	
Age of menarche, years					0.193
≤15	252 (71.8)	98.3	88.6	76.6	
>15	50 (14.2)	98.0	83.8	69.8	
Unknown	49 (14.0)				
Fertility status					0.849
Yes	323 (92.0)	98.4	87.4	73.4	
No	27 (7.7)	96.2	86.5	71.9	
Unknown	1 (0.3)				
HBV infection					0.592
Yes	9 (2.6)	100.0	70.0	70.0	
No	342 (97.4)	98.2	87.8	73.4	
Family history					0.986
BC	8 (2.3)	100.0	100.0	66.7	
Other cancer types	13 (3.7)	100.0	88.9	74.1	
No	330 (94.0)	98.1	87.0	73.5	

[a]Patients with bone metastasis at diagnosis; [b]patients received simple resection in another hospital prior to administration; [c]censored data. OS, overall survival; Tis, tumor in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma *in situ*; HER-2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; BC, breast cancer; HBV, hepatitis B virus.

Table IV. Cox regression analysis for predicting visceral metastasis-free survival.

			95% CI	
Characteristic	HR	P-value	Lower	Upper
N stage		<0.001		
N1/N0	2.977	0.025	1.148	7.722
N2/N0	4.477	0.003	1.641	12.211
N3/N0	8.695	<0.001	0.296	22.937
Molecular subtype		0.027		
Luminal B/luminal A	1.426	0.536	0.463	4.390
HER-2/luminal A	2.965	0.007	1.342	6.552
Triple-negative/luminal A	2.763	0.017	1.201	6.353
Age, years				
<35/≥35	3.739	<0.001	1.905	7.338

HR, hazard ratio; CI, confidence interval; HER-2, human epidermal growth factor receptor 2.

Table V. Cox regression analysis for predicting disease-free survival.

			95% CI	
Characteristic	HR	P-value	Lower	Upper
N stage		0.004		
N1/N0	1.742	0.082	0.933	3.253
N2/N0	2.295	0.009	1.230	4.284
N3/N0	3.041	0.001	1.621	5.704
Molecular subtype		0.002		
Luminal B/luminal A	1.846	0.090	0.908	3.751
HER-2/luminal A	3.030	<0.001	1.707	5.379
Triple-negative/luminal A	1.944	0.029	1.071	3.528

HR, hazard ratio; CI, confidence interval; HER-2, human epidermal growth factor receptor 2.

Table VI. Cox regression analysis for predicting overall survival.

			95% CI	
Characteristic	HR	P-value	Lower	Upper
N stage		0.029		
N1/N0	1.052	0.920	0.392	2.822
N2/N0	1.888	0.193	0.725	4.921
N3/N0	3.210	0.009	1.347	7.653
Molecular subtype		0.006		
Luminal B/luminal A	0.968	0.959	0.276	3.399
HER-2/luminal A	2.809	0.009	1.290	6.119
Triple-negative/luminal A	3.262	0.003	1.504	7.075
Neoadjuvant chemotherapy				
Yes/no	2.722	0.006	1.336	5.543

HR, hazard ratio; CI, confidence interval; HER-2, human epidermal growth factor receptor 2.

proportional hazard regression analysis was performed. As presented in Tables VII-IX, the range of the HR was 1.692-2.239 for VFS with P≤0.005, 1.910-2.879 for DFS with P≤0.003 and 1.938-2.652 for OS with P≤0.003. Therefore, risk scores and nonograms were demonstrated to be reliable for predicting VFS, DFS and OS time in young patients with BC.

Discussion

China has a high prevalence of young patients with BC, who exhibit a poor prognosis (2). A number of studies have demonstrated that age (3,6,8,9,20) and molecular subtype (4,7) are associated with survival in these patients, in addition to a larger tumor size, higher incidence of lymph node involvement (4,5) and higher incidence of poorly differentiated tumors (4,5). However, to the best of our knowledge, a prediction model for these patients has not been established. Nomograms are widely used to present prediction models for a number of cancer types (21-23). Due to their distinctness and clarity, nomograms are useful for patients to understand the prognosis of their disease and for doctors to decide the most appropriate treatment protocol. Nomograms have been generated for BC to predict the outcome of patients who have undergone neoadjuvant chemotherapy (24) and of patients with advanced tumors (21). In addition, nomograms have been established to predict axillary lymph node status (25) and loco-regional recurrence (26), thus assisting surgeons with the decision of surgical type. The current study created and displayed survival models as nomograms to predict the outcome of young patients with BC.

In the current study, the prediction model for DFS included two independent variables, N stage and molecular subtype, which was consistent with a previous study (8). N stage represented the tumor burden and the capacity of metastasis, while the molecular subtype represented the biological characteristics of the tumor. Patients with the luminal A subtype exhibited the longest DFS time, while patients with the HER-2$^+$ subtype exhibited the worst prognosis. A significant difference was identified in the DFS between these molecular subtypes, as demonstrated in previous studies (8,27).

Notably, to the best of our knowledge, the current study is the first to introduce the concept of VFS for breast cancer, which is defined as the time from radical surgery to the first visceral metastasis or mortality. Previous studies have typically used the concept of distant recurrence-free survival (DDFS) (28), which is defined as the time from radical surgery to the first distant metastasis or mortality. The difference between DDFS and VFS is the metastatic sites. Bone metastasis and distant lymph node metastasis are included in DDFS, but not in VFS. Savci-Heijink *et al* (29) reported that BC cases without visceral metastasis exhibited improved survival rates

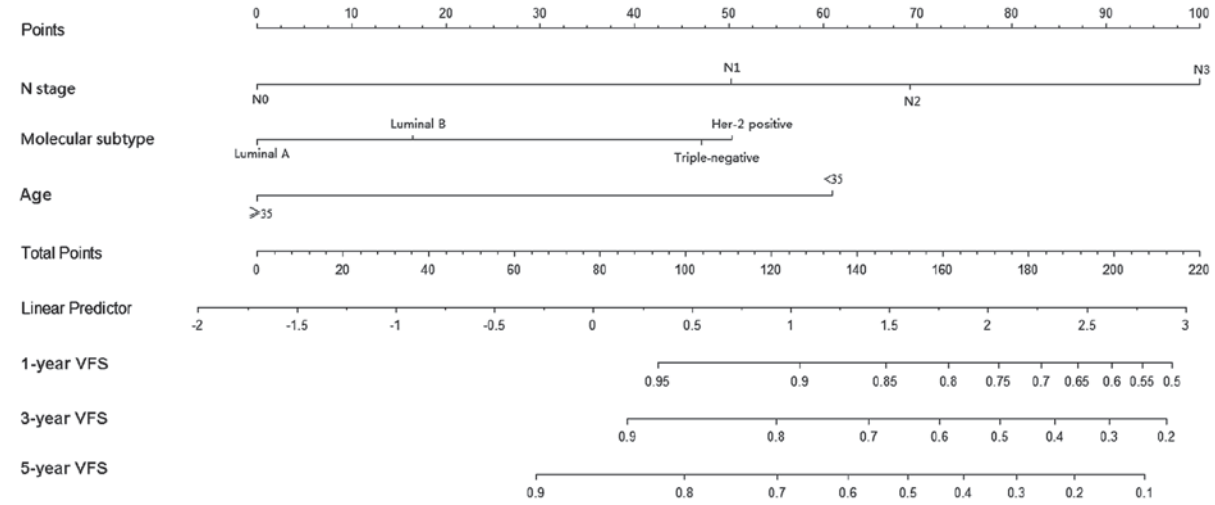

Figure 1. Nomogram for predicting VFS in young patients with breast cancer. VFS, visceral metastasis-free survival; HER-2, human epidermal growth factor receptor 2.

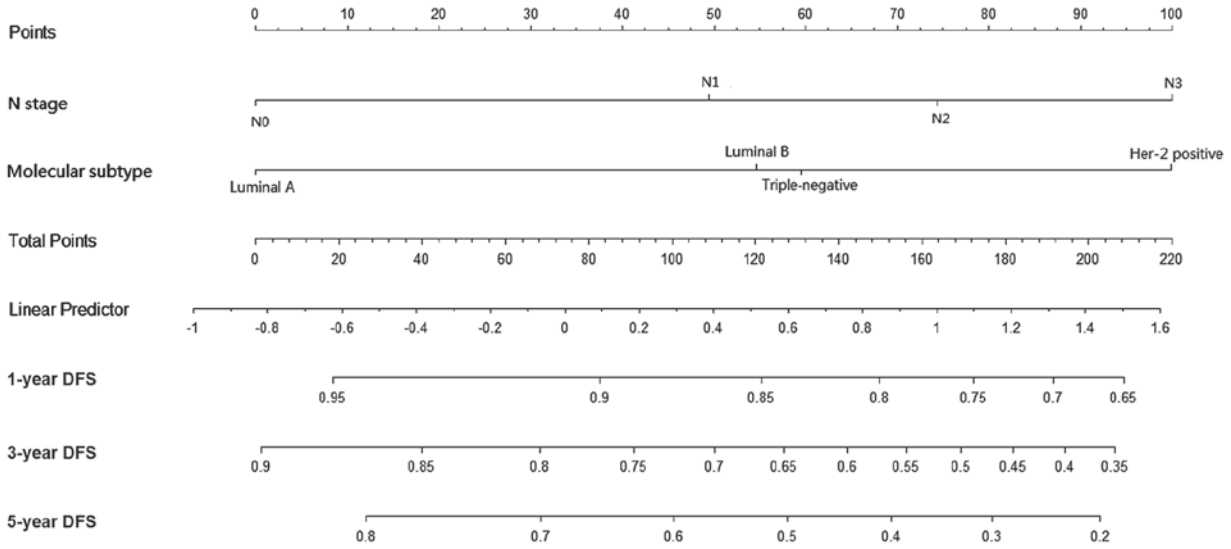

Figure 2. Nomogram for predicting DFS in young patients with breast cancer. DFS, disease-free survival; HER-2, human epidermal growth factor receptor 2.

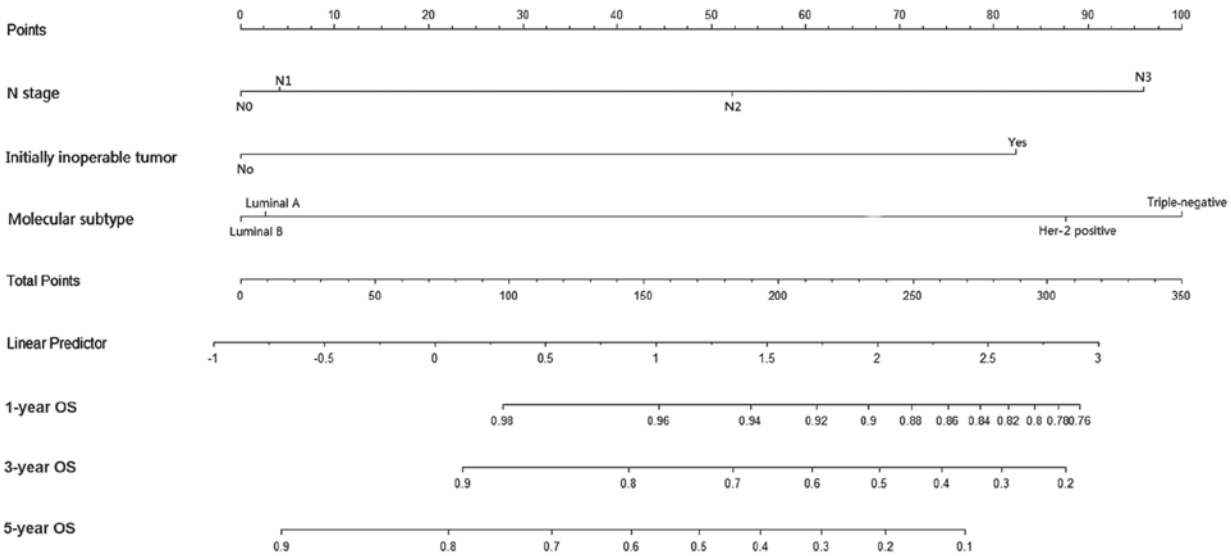

Figure 3. Nomogram for predicting OS in young patients with breast cancer. OS, overall survival; HER-2, human epidermal growth factor receptor 2.

Table VII. Internal validation of risk scores for predicting visceral metastasis-free survival in randomly sampled patients by Cox regression analysis.

Subset no.	200 cases		250 cases		300 cases	
	P-value	HR	P-value	HR	P-value	HR
1	0.002	1.836	<0.001	1.861	<0.001	2.113
2	<0.001	1.759	<0.001	2.388	<0.001	2.239
3	<0.001	2.025	<0.001	1.834	<0.001	1.942
4	<0.001	2.157	<0.001	1.812	<0.001	1.846
5	<0.001	2.041	0.002	1.666	<0.001	2.109
6	0.005	1.692	<0.001	1.915	<0.001	1.942
7	<0.001	1.860	<0.001	2.371	<0.001	1.968
8	<0.001	2.003	<0.001	2.146	<0.001	1.990
9	<0.001	1.902	0.001	1.656	<0.001	1.823
10	0.001	1.764	<0.001	2.177	<0.001	1.786

HR, hazard ratio.

Table VIII. Internal validation of risk scores for predicting disease-free survival in randomly sampled patients by Cox regression analysis.

Subset no.	200 cases		250 cases		300 cases	
	P-value	HR	P-value	HR	P-value	HR
1	<0.001	2.228	<0.001	2.141	<0.001	2.482
2	<0.001	2.296	<0.001	2.646	<0.001	2.489
3	<0.001	2.422	0.001	2.023	<0.001	2.585
4	<0.001	2.352	0.001	2.059	<0.001	2.300
5	<0.001	2.799	<0.001	2.131	<0.001	2.879
6	0.001	2.354	<0.001	2.244	<0.001	2.601
7	0.001	2.072	<0.001	2.473	<0.001	2.492
8	0.003	1.910	<0.001	2.724	<0.001	2.493
9	<0.001	2.212	0.001	1.992	<0.001	2.019
10	<0.001	2.646	<0.001	2.447	<0.001	2.204

HR, hazard ratio.

Table IX. Internal validation of risk scores for predicting overall survival in randomly sampled patients by Cox regression analysis.

Subset no.	200 cases		250 cases		300 cases	
	P-value	HR	P-value	HR	P-value	HR
1	0.003	1.938	<0.001	2.208	<0.001	2.253
2	<0.001	2.442	<0.001	2.986	<0.001	2.141
3	<0.001	2.323	<0.001	2.071	<0.001	2.338
4	<0.001	2.652	<0.001	2.243	<0.001	2.052
5	<0.001	2.496	<0.001	2.007	<0.001	2.269
6	<0.001	2.090	<0.001	2.181	<0.001	2.369
7	<0.001	2.243	<0.001	2.396	<0.001	2.175
8	<0.001	2.273	<0.001	2.516	<0.001	2.353
9	0.001	2.106	<0.001	2.365	<0.001	2.03
10	<0.001	2.241	<0.001	2.249	<0.001	2.039

HR, hazard ratio.

compared with those with visceral metastasis. It was identified that patients with local relapse, lymph node metastasis and bone metastasis exhibited improved survival rates compared with patients with visceral metastasis. Therefore, the current study assumed that VFS was a valuable measurement for prognostic prediction. The current study identified that VFS was associated with molecular subtype, N stage and age, but not local relapse, bone metastasis and lymph node metastasis. This result differed from the prediction model for DFS time, as age at diagnosis was identified as an independent predictor for VFS time. Previous studies revealed that a younger age is associated with a more aggressive cancer that is more likely to metastasize to visceral organs (3-6) Additionally, a previous study demonstrated that age is an independent predictor of DFS and OS time (30). The current study also demonstrated that age (<35 years) was negatively associated with VFS.

Furthermore, molecular subtype has previously been associated with patterns of metastasis (29,31). Patients with certain molecular subtypes, including ER^- and $HER\text{-}2^+$ subtypes, have been associated with visceral metastasis, while patients with an ER^+ subtype have been associated with bone metastasis (29,31,32). The current study revealed that patients with the luminal A subtype experienced the longest VFS time, while patients with the $HER\text{-}2^+$ subtype experienced the shortest VFS time and the highest frequency of visceral metastasis. The unfavorable outcome of patients with the $HER\text{-}2^+$ subtype may partially be due to the low percentage of patients in this group who experienced targeted treatment. However, by July 2017 >75,000 patients with $HER\text{-}2^+$ breast cancer in China benefited from the Herceptin Patient Assistance Program and received targeted treatment (unpublished data), which may increase their survival rates.

The current study identified that N stage, molecular subtype and neoadjuvant chemotherapy were associated with OS. N stage and molecular subtype have been associated with OS in previous studies (8,28,29,31). However, a significant association between OS and neoadjuvant chemotherapy was also identified in the current study. To the best of our knowledge, this result has not previously been reported. In the current study, only 1 patient received neoadjuvant chemotherapy prior to breast conservation surgery. The remaining 45 cases received neoadjuvant chemotherapy due to the presence of initially inoperable tumors. The prediction model demonstrated that patients with a $HER\text{-}2^+$ subtype, an advanced N stage or an initially inoperable tumor exhibited unfavorable OS.

According to the survival analysis, nomograms were created and risk scores (19) were calculated based on the Cox regression coefficients for VFS, DFS and OS time. Internal validation was performed in patients randomly sampled

from the total population. This validation demonstrated that the risk scores were associated with VFS, DFS and OS time. This suggests that the nomograms constructed following Cox regression analysis were reliable. However, the lack of a validation cohort is a limitation of the current study. Future studies should collect a larger number of cases to further validate the nomograms.

In conclusion, the current study constructed and validated survival models displayed as nomograms to predict VFS, DFS and OS time in young patients with BC using retrospective data from patients <40 years old at diagnosis. In addition, the concept of VFS was introduced. Molecular subtype and N stage were identified as independent predictors for VFS, DFS and OS time. Age at diagnosis was revealed to independently predict VFS and neoadjuvant chemotherapy was identified as an unfavorable factor for OS. Risk scores based on these survival models were established for young patients with BC. These survival models were validated and the current study recommends their use in the survival analysis of young patients with BC in the future.

Acknowledgements

The authors would like to thank Professor William Au from Shantou University Medical College (Shantou, China) for providing assistance in editing the original manuscript.

Funding

The current study was supported by the Shantou Health and Technology Program (grant no. 123).

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HL and FZ designed the study. FZ conducted the statistical analysis. HL and FZ analyzed and interpreted the data. HL, FZ, DZ and LW were involved in the data acquisition. HL, FZ, DZ and LW wrote the manuscript. All authors have read and approved the final submitted manuscript. HL takes final responsibility.

Ethics approval and consent to participate

Written informed consent was obtained from all participants for the use of clinicopathological information. The current study was approved by the Ethics Committee of the Cancer Hospital of Shantou University Medical College (Guangdong, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO and Jemal A: International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 24: 1495-1506, 2015.
2. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, Chen WQ, Shao ZM and Goss PE: Breast cancer in China. Lancet Oncol 15: E279-E289, 2014.
3. Tang LC, Yin WJ, Di GH, Shen ZZ and Shao ZM: Unfavourable clinicopathologic features and low response rate to systemic adjuvant therapy: Results with regard to poor survival in young Chinese breast cancer patients. Breast Cancer Res Treat 122: 95-104, 2010.
4. Zabicki K, Colbert JA, Dominguez FJ, Gadd MA, Hughes KS, Jones JL, Specht MC, Michaelson JS and Smith BL: Breast cancer diagnosis in women <or=40 versus 50 to 60 years: Increasing size and stage disparity compared with older women over time. Ann Surg Oncol 13: 1072-1077, 2006.
5. Goksu SS, Tastekin D, Arslan D, Gunduz S, Tatli AM, Unal D, Salim D, Guler T and Coskun HS: Clinicopathologic features and molecular subtypes of breast cancer in young women (age </=35). Asian Pac J Cancer prev 15: 6665-6668, 2014.
6. Tjokrowidjaja A, Lee CK, Houssami N and Lord S: Metastatic breast cancer in young women: A population-based cohort study to describe risk and prognosis. Intern Med J 44: 764-770, 2014.
7. Keegan TH, DeRouen MC, Press DJ, Kurian AW and Clarke CA: Occurrence of breast cancer subtypes in adolescent and young adult women. Breast Cancer Res 14: R55, 2012.
8. Chen HL, Ding A and Wang FW: Prognostic effect analysis of molecular subtype on young breast cancer patients. Chin J Cancer Res 27: 428-436, 2015.
9. Liedtke C, Rody A, Gluz O, Baumann K, Beyer D, Kohls EB, Lausen K, Hanker L, Holtrich U, Becker S and Karn T: The prognostic impact of age in different molecular subtypes of breast cancer. Breast Cancer Res Treat 152: 667-673, 2015.
10. Azim HA Jr, Nguyen B, Brohee S, Zoppoli G and Sotiriou C: Genomic aberrations in young and elderly breast cancer patients. BMC Med 13: 266, 2015.
11. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ and 10th St. Gallen conference: Progress and promise: Highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18: 1133-1144, 2007.
12. Plichta JK, Rai U, Tang R, Coopey SB, Buckley JM, Gadd MA, Specht MC, Hughes KS, Taghian AG and Smith BL: Factors associated with recurrence rates and long-term survival in women diagnosed with breast cancer ages 40 and younger. Ann Surg Oncol 23: 3212-3220, 2016.
13. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I and Lindman H: Breast cancer in young women: Poor survival despite intensive treatment. PLoS One 4: e7695, 2009.
14. Hearne BJ, Teare MD, Butt M and Donaldson L: Comparison of nottingham prognostic index and adjuvant online prognostic tools in young women with breast cancer: Review of a single-institution experience. BMJ open 5: e005576, 2015.
15. Karihtala P, Winqvist R, Bloigu R and Jukkola-Vuorinen A: Long-term observational follow-up study of breast cancer diagnosed in women </=40 years old. Breast 19: 456-461, 2010.
16. Edge SB and Compton CC: The American joint committee on cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17: 1471-1474, 2010.
17. Alco G, Bozdogan A, Selamoglu D, Pilanci KN, Tuzlali S, Ordu C, Igdem S, Okkan S, Dincer M, Demir G and Ozmen V: Clinical and histopathological factors associated with Ki-67 expression in breast cancer patients. Oncol Lett 9: 1046-1054, 2015.
18. Wang S, Saboorian MH, Frenkel E, Hynan L, Gokaslan ST and Ashfaq R: Laboratory assessment of the status of Her-2/neu protein and oncogene in breast cancer specimens: Comparison of immunohistochemistry assay with fluorescence in situ hybridisation assays. J Clin Pathol 53: 374-381, 2000.
19. Shukla S, Pia Patric IR, Thinagararjan S, Srinivasan S, Mondal B, Hegde AS, Chandramouli BA, Santosh V, Arivazhagan A and Somasundaram K: A DNA methylation prognostic signature of glioblastoma: Identification of NPTX2-PTEN-NF-kappaB nexus. Cancer Res 73: 6563-6573, 2013.
20. Tang LC, Jin X, Yang HY, He M, Chang H, Shao ZM and Di GH: Luminal B subtype: A key factor for the worse prognosis of young breast cancer patients in China. BMC Cancer 15: 201, 2015.

21. Lee CK, Hudson M, Stockler M, Coates AS, Ackland S, Gebski V, Lord S, Friedlander M, Boyle F and Simes RJ: A nomogram to predict survival time in women starting first-line chemotherapy for advanced breast cancer. Breast cancer Res Treat 129: 467-476, 2011.
22. Vernerey D, Huguet F, Vienot A, Goldstein D, Paget-Bailly S, Van Laethem JL, Glimelius B, Artru P, Moore MJ, André T, *et al*: Prognostic nomogram and score to predict overall survival in locally advanced untreated pancreatic cancer (PROLAP). Br J Cancer 115: 281-289, 2016.
23. Liang W, Zhang L, Jiang G, Wang Q, Liu L, Liu D, Wang Z, Zhu Z, Deng Q, Xiong X, *et al*: Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. J Clin Oncol 33: 861-869, 2015.
24. Keam B, Im SA, Park S, Nam BH, Han SW, Oh DY, Kim JH, Lee SH, Han W, Kim DW, *et al*: Nomogram predicting clinical outcomes in breast cancer patients treated with neoadjuvant chemotherapy. J Cancer Res Clin Oncol 137: 1301-1308, 2011.
25. Qiu SQ, Zeng HC, Zhang F, Chen C, Huang WH, Pleijhuis RG, Wu JD, van Dam GM and Zhang GJ: A nomogram to predict the probability of axillary lymph node metastasis in early breast cancer patients with positive axillary ultrasound. Sci Rep 6: 21196, 2016.
26. Witteveen A, Vliegen IM, Sonke GS, Klaase JM, MJ IJ and Siesling S: Personalisation of breast cancer follow-up: A time-dependent prognostic nomogram for the estimation of annual risk of locoregional recurrence in early breast cancer patients. Breast Cancer Res Treat 152: 627-636, 2015.
27. Song N, Choi JY, Sung H, Jeon S, Chung S, Park SK, Han W, Lee JW, Kim MK, Lee JY, *et al*: Prediction of breast cancer survival using clinical and genetic markers by tumor subtypes. PLoS One 10: e0122413, 2015.
28. Hennigs A, Riedel F, Gondos A, Sinn P, Schirmacher P, Marmé F, Jäger D, Kauczor HU, Stieber A and Lindel K, *et al*: Prognosis of breast cancer molecular subtypes in routine clinical care: A large prospective cohort study. BMC Cancer 16: 734, 2016.
29. Savci-Heijink CD, Halfwerk H, Hooijer GK, Horlings HM, Wesseling J and van de Vijver MJ: Retrospective analysis of metastatic behaviour of breast cancer subtypes. Breast Cancer Res Treat 150: 547-557, 2015.
30. Zhao Y, Dong X, Li R, Song J and Zhang D: Correlation between clinical-pathologic factors and long-term follow-up in young breast cancer patients. Transl Oncol 8: 265-272, 2015.
31. Kast K, Link T, Friedrich K, Petzold A, Niedostatek A, Schoffer O, Werner C, Klug SJ, Werner A, Gatzweiler A, *et al*: Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 150: 621-629, 2015.
32. Bartmann C, Diessner J, Blettner M, Häusler S, Janni W, Kreienberg R, Krockenberger M, Schwentner L, Stein R, Stüber T, *et al*: Factors influencing the development of visceral metastasis of breast cancer: A retrospective multi-center study. Breast 31: 66-75, 2017.