Loco-Regional Recurrence Trend and Prognosis in Young Women With Breast Cancer According to Molecular Subtypes

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Research

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Abstract

Purpose The number of young patients diagnosed with breast cancer is on the rise. We studied the rate trend of local recurrence (LR) and regional recurrence (RR) in young breast cancer (YBC) patients and outcomes among these patients based on molecular subtypes.

Methods A retrospective cohort study was conducted based on data from Tianjin Medical University Cancer Institute and Hospital for patients ≤ 35 years of age with pathologically-confirmed primary invasive breast cancer surgically treated between 2006 and 2014. Patients were categorized according to molecular subtypes on the basis of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. The 5-year rates for LR, RR, and distant metastases were estimated by Kaplan-Meier statistics. Nelson-Aalen cumulative-hazard plots were used to describe local recurrence- and distant metastases-free intervals.

Results We identified 25,284 patients with a median follow-up of 82 months, of whom 1099 (4.3%) were YBC patients ≤ 35 years of age. The overall 5-year local, regional, and distant recurrence rates in YBC patients were 6.7%, 5.1%, and 16.6%, respectively. The LR and RR rates demonstrated a decreasing trend over time ($P=0.028$ and $P=0.015$, respectively). We found that early-stage breast cancer and less lymph node metastases increased over time ($P=0.004$ and $P=0.007$, respectively). Patients with HR-/HER2+ status had a significantly higher LR (HR 20.4; 95% CI, 11.8-35.4) and DM (HR 37.2; 95% CI, 24.6-56.3) at 10 years. In the overall population, the 5-year survival of YBC patients exceeded 90%.

Conclusion The rates of LR and RR with YBC patients demonstrated a downward trend and the proportion of early-stage breast cancer increased between 2006 and 2014. We report that the outcomes varied with molecular subtypes and patients with HR-/HER2+ status had the worst survival.

Introduction

It has been estimated that 4% of females < 40 years of age were diagnosed with breast cancer in the United States in 2017 and breast cancer is the leading cause of cancer deaths among women 20–59 years of age^{1,2}. Prior studies have revealed that young age is a known risk prognostic factor for breast cancer patients^{3–8}. This finding is reflected by larger tumors, higher grade, advanced stage, more lymph node metastases, a higher prevalence of human epidermal growth factor receptor (HER)2 over-expression, and estrogen receptor (ER)-negativity in young women with breast cancer^{4,5,7}. With respect to detrimental gene expression, Azim et al.⁹ reported higher expression of gene signatures related to proliferation, stem cells, and endocrine resistance in tumors associated with young age. In addition, higher expression of epithelial growth factor receptor (EGFR) mRNA, which BRCA1/2-associated breast tumors overexpress¹⁰, is a significant predictor of poor prognosis in young women⁵.

The relative risk of loco-regional recurrence (LRR) increases by 7% for every year of decrease in age¹¹. Previous research showed that young women with breast cancer who undergo breast-conserving surgery (BCS) have higher rates of developing LRR compared with women who undergo mastectomy, but the overall survival (OS) is not affected^{12,13}. Despite higher rates of LRR in young patients, several studies had shown a declining trend in the LRR rate over the past two decades^{14–16}. In addition, there has been a significant decline in the occurrence of distant metastases (DM)^{17,18} and increase in the overall survival over the last years in young breast cancer (YBC) patients owing to the evolution of improved adjuvant systemic treatment and raising consciousness of physical examination^{19,20}.

Breast cancer arising in young women is more likely to develop into more aggressive tumor subtypes, including a greater proportion of triple-negative and HER2 over-expressing subtypes^{5,6,8}. Accumulating evidence has demonstrated a strong relationship between molecular subtypes and prognosis in YBC patients^{21–32}. A number of reports have shown a worse OS rate in young women with luminal B breast cancer^{27,28,31,32}, whereas other research has suggested that triple-negative and HER2 over-expressing tumors are strong predictors of disease recurrence^{29,30,33}. Therefore, larger, well-designed prospective clinical studies are needed to explore this relationship.

The trend in LRR rates in YBC patients in recent years has not been established. We therefore evaluated the trend in LRR and determine the impact of molecular subtypes on LRR and OS in young women diagnosed with breast cancer.

Patients And Methods

Patients

This was a retrospective study that included breast cancer patients ≤ 35 years of age at Tianjin Medical University Cancer Institute and Hospital from January 2006 to December 2014. There were 25,284 patients diagnosed with breast cancer in our hospital during the 9-year period, of whom 1307 were ≤ 35 years of age. Patients ≤ 35 years of age with pathologically-confirmed primary invasive breast cancer and

underwent surgery from 2006-2014 were selected for our study. Subjects with non-invasive cancer (54 cases), including ductal carcinoma *in situ* (16 cases), primary metastatic breast cancer (20 cases), and bilateral primary breast cancer (42 cases), were excluded. We also excluded patients who did not have electronic medical records in our institution and who could not be contacted by telephone or mail to confirm survival status (92 cases). A total of 1099 young women with breast cancer met the inclusion criteria for our study.

Methods

We collected the following patient demographics: age; family history of breast cancer; reproductive history; and breastfeeding history. The tumor characteristics included tumor size, stage, lymph node status, histologic grade, and pathologic type. We classified cancer into five molecular subtypes according to hormone receptor (HR) and HER2 status, as follows: HR-positive/Her2-negative; HR-positive/Her2-positive; HR-negative/Her2-positive; HR-negative/Her2-negative; and unknown. Molecular subtype was defined by immunohistochemical staining features of HR (estrogen receptor [ER] and/or progesterone receptor [PR]) and HER2. Categorization based on staining features was as follows: ER and PR staining < 1% was defined as negative; ER and PR staining $\geq$ 1% was defined as positive³⁴; HER2 0/1 was defined as negative; and HER2 2+ was defined as negative or positive by fluorescence *in situ* hybridization (FISH) and positive by HER2 3+. Information regarding adjuvant chemotherapy, radiotherapy, hormonal therapy, ovarian function suppression, and trastuzumab therapy were obtained from the hospital and follow-up records.

Variable Definitions

The follow-up data for LR, RR, DM, and OS were abstracted from the electronic medical records, paper medical documents, telephone, and mail. For patients at the time of contact had died, available family members provided the requested information. Follow-up started on the day of surgery to the date of any type of recurrence, death, the last contact according to the medical record, or in-person contact. LR was defined as recurrence of ipsilateral breast cancer after breast-conserving surgery or chest wall recurrence after mastectomy. RR referred to the occurrence of tumor in the ipsilateral regional lymph nodes, including the axillary, infra- or supra-clavicular or internal mammary lymph nodes. DM was defined as recurrence beyond LR and RR. We defined OS as the time from surgery to death from any cause or last follow-up. The local recurrence-free interval (LRFI) was defined as the interval from surgery to local recurrence or the date of last follow-up.

Statistical analysis

Descriptive statistics were performed to examine the demographic characteristics of young patients surgically treated between 1 January 2006 and 31 December 2014. The percentage of clinicopathologic and therapeutic regimen among YBC patients were compared for the different molecular subtypes using a chi-square test. Moreover, tumor characteristics for all YBC patients according to the time of diagnosis were assessed over time.

We used Kaplan-Meier survival estimates to calculate overall 5-year LR, RR, and DM rates for the young patients with breast cancer and the trends of LR, RR and DM over time were assessed by using linear regression analysis. Moreover, local, regional, and distant recurrence rates of YBC patients treated between 2006 and 2014 according to various biomarker subtypes were calculated. We performed univariate and multivariate Cox proportional hazard model to examine the influence of different variables on LR, RR, and DM. Hazard ratios and the associated 95% confidence intervals (CIs) were obtained based on Cox regression analysis. The OS was summarized by Kaplan-Meier survival curves according to tumor subtypes and compared using log-rank test univariate analyses. Nelson-Aalen cumulative-hazard plots were used to describe the LRFI and distant metastases-free interval (DMFI). Subsequently, 5- and 10-year estimates of LRFI, regional recurrence-free interval (RRFI), DMFI, and OS according to various molecular subtypes were calculated using Kaplan-Meier survival analysis. P values <0.05 were considered statistically significant and all tests were two-tailed. Analyses were performed using SPSS 22.0 and STATA software 14.1.

Results

Patients Characteristics

A total of 1099 YBC patients who were surgically treated were enrolled in our study from 2006-2014. This cohort accounted for 4.3% of the total population of patients who were diagnosed with breast cancer in our hospital during the 9-year period (n=25,284). The median follow-up time was 82 months. The demographic characteristics of the YBC patients are shown in Table I. Seventy-five percent of the patients had early-stage breast cancer (stages I and II). Among the patients, 54.0%, 10.9%, 6.8%, and 18.3% of patients were HR+/HRE2-, HR+/Her2+, HR-/Her2+, and HR-/Her2- subtypes, respectively. The baseline clinicopathologic and treatment characteristics differed by tumor subtype, as shown in Table II. Patients with HER2 2+ status who were not subsequently detected by FISH were classified as unknown subtype. HR+/HER2- tumors tended to be smaller in size (P=0.007), lower stage (P<0.001), and lower histologic grade (P<0.001) compared with the other subtypes. Patients with HR-/HER2+ status were likely to have larger tumors (P=0.007) and more possibilities for radiotherapy treatment (P<0.001).

Patients with HER2-negative breast cancer presented with fewer lymph node metastases, while HER2-positive tumors tended to have > 9 lymph node metastases ($P<0.001$). Compared with HER2-positive tumors, patients with HER2-negative tumors generally underwent breast-conserving surgery ($P=0.002$).

In addition, we studied the distribution of tumor characteristics for all YBC patients over time shown in Table III. Tumor size, histologic grade, and pathologic type did not vary significantly between 2006 and 2014. Of note, there were distinct proportional shifts of stage and lymph node metastases over time ($P=0.004$ and $P=0.007$, respectively). The proportion of N1 increased ($P=0.016$ using linear regression analyses), while N2 and N3 showed a declining trend, although no significant difference was detected using linear regression analyses. The percentage of patients with stage II breast cancer was higher and the percentage of patients with breast cancer stage III trended down over time.

Recurrence Rates

The overall 5-year LR, RR, and DR rates in YBC patients were 6.7%, 5.1%, and 16.6%, respectively. We used linear regression analyses to evaluate the time trend of recurrence rates over the 9-year period. The LR and RR rates demonstrated a decreasing trend over time ($P=0.028$ and $P=0.015$, respectively). The DM rate also declined, although the difference was not statistically significant ($P=0.228$), as is shown in Table IV.

There were statistically significant differences in the LR and DM rates in patients with various tumor subtypes ($P=0.002$ and $P=0.003$, respectively; Fig. 1). Patients with HR-/HER2+ tumors had the highest recurrence rate compared with the other subtypes (LR: 17.3%, RR: 9.3%, and DM: 30.7%). Patients with HR+/HER2- status displayed the lowest LR rate (5.6%), whereas the triple-negative subtype showed the lowest DM rate (13.4%). There were 194 patients with HER2-positive breast cancer and 83 patients (42.8%) received targeted therapy after surgery.

We used univariate and multivariate Cox proportional hazard models to analysis the prognostic factors, as shown in Table V. Patients with larger tumors and more lymph node metastases had increased HR in univariate and multivariate analyses for LR ($P<0.01$). Based on the univariate analysis, patients with the HR-/HER2+ subtype displayed higher HR for LR and DM than patients with the HR+/HER2- subtype (LR, 3.5 [1.8-6.7] and DM, 1.9 [1.2-2.9]; all $P<0.01$).

Survival Outcomes

HR-/HER2+ patients had the worse OS compared to patients with the other subtypes ($P<0.001$; Fig. 2). Table VI lists the relapse and OS for patients with various molecular subtypes. HR-/HER2+ patients had the worst LRFI, RRFI, DMFI, and OS compared to patients with the other subtypes. The median follow-up time was 82 months (range, 5-156 months). In the overall population, the 5-year survival of young patients with breast cancer surgically treated in our institution exceeded 90%. The 5-year OS for patients with HR+/HER2-, HR+/HER2+, HR-/HER2+, and HR-/HER2- was 94.3% (95% CI, 92.0%-95.9%), 87.3% (95% CI, 79.5%-92.3%), 77.9% (95% CI, 66.5%-85.8%), and 92.7% (95% CI, 88.0%-95.6%), respectively. The 5-year LRFI and RRFI were highest in patients with the HR+/HER2- subtype (95.6% [95% CI, 94.0%-97.0%] and 95.5% [95% CI, 93.4%-97.0%], respectively). For patients with triple-negative tumors, the 10-year DMFI was > 85%, which was higher than the other molecular subtypes. Fig. 3 and Fig. 4 show the Nelson-Aalen cumulative hazard rates for LRFI and DMFI by tumor subtype. Patients with HR-/HER2+ status had a significantly higher LR (HR, 20.4; 95% CI, 11.8-35.4) and DM (HR, 37.2; 95% CI, 24.6-56.3) at 10 years.

There were 194 women with HER2-positive status and 83 patients received trastuzumab therapy, of whom 20 (24.1%) relapsed after surgery in the current study. Sixty-three women declined trastuzumab therapy and post-operative recurrences occurred in 21 patients (33.3%). In women with HER2-positive cancers, the relapse rate was not significantly different between those who did and did not receive trastuzumab ($p=0.326$).

Discussion

We found a statistically different decreasing trend in the LR and RR rates over time in this large retrospective cohort study of young women with operable invasive breast cancer. This research also revealed that the LR and DM rates varied with molecular subtype. Tumor size, lymph nodes metastases, and hormonal therapy were associated with LR, while lymph node metastases and suppression of ovarian function impacted RR based on the multivariate analysis. The 5-year OS of YBC patients was > 90%, with HR-/HER2+ tumors having the worst survival.

The overall 5-year rates of developing LR, RR, and DM were 6.7%, 5.1%, and 16.6%, respectively. Several studies have reported various rates of LRR of YBC patients. LR occurred in 5.4% of the entire population (7.6% of those who underwent breast-conserving surgery [BCS] and 2.6% of those who underwent a mastectomy). An RR of 0.6% after BCS versus 2.6% after mastectomy during 11 years of follow-up in women with breast cancer ≤ 35 of age were collected from the Ontario Cancer Registry between 1994 and 2003¹³. A study conducted by Aalders et al.¹⁴ reported that young patients < 35 years of age with early-stage breast cancer had a 5-year cumulative incidence of LR, RR, and DM of 3.5%, 3.7%, and 13.9% between 2003 and 2008, respectively. Another study reported a cohort of 3024 patients 18–40 years of age diagnosed with breast cancer a 5-year LRR rate of 2.63% after mastectomy versus 5.33% after BCS (HR, 3.39; 95% CI, 2.03–5.66; $P<0.001$)¹². The previous studies likely showed lower rates of LRR because early-stage breast cancer accounted for a large proportion of the study subjects. Patients

with stages I and II breast cancer made up 75% of the cohort in our study, while the percentage reached 95% in the study conducted by Aalders et al.¹⁴.

The rates of LR and RR demonstrated a significant decreasing trend during the period of our study. The results of our research were consistent with previous studies^{14–16, 21, 35}. A study conducted by Cossetti et al.²¹ divided 7178 patients with biopsy-proven stage I–III breast cancer into cohort 1 (C1) and 2 (C2) who were diagnosed between 1986 and 1992, and mid-2004 and 2008, respectively. The authors demonstrated that the hazard rate of relapse was nearly halved in all yearly intervals to year 9 in C2 compared with C1 among the overall population²¹. The patients < 40 years of age in this research accounted for 13.2% of patients, and a subsequent study involving patients < 35 years of age showed overall 5-year rates for LR and RR decreased over time¹⁴. We studied the time trend of tumor characteristics per incidence year of patients and revealed that the proportion of stages I and II breast cancer increased, while stage III showed a downward trend over the 9 years. This finding might explain, in part, the decreasing trend of recurrence rates over time.

We observed a downtrend in the recurrence of DM over time, although the difference was not statistically significant. Previous studies have reported similar results^{14, 17, 36}. Therefore, we suggest that the improvement in OS among patients with breast cancer is closely associated with the lower DM rates in recent years^{16, 19, 37, 38}.

Patients with HR-/HER2+ tumors (HER2 over-expressing tumors) had the highest LR rates, while HR+/HER2- tumors (luminal tumors) displayed the lowest LR rates among the entire cohort. A systematic review identifying patients from 15 studies appraised the effect of molecular subtype on LRR according to the type of surgery and the authors suggested patients with triple-negative and HER2 over-expressing subtypes were at high risk of developing LRR, and luminal tumors exhibited the lowest LRR rates²⁵, which was in agreement with our findings. A cohort of 394 early-stage invasive breast cancer patients undergoing BCS were classified as luminal A, luminal B, HER-2, and basal phenotype. The reported crude LRR rates of the basal phenotype were highest (17.3%), followed by HER-2 (15.4%), luminal B (8.7%), and luminal A (5%)²⁴. A five-biomarker panel (ER, PR, HRE-2, CK5/6, and EGFR) was used to categorize the tumors, which is not a commonly intrinsic molecular phenotype of breast cancer, and therefore it is not useful clinically. However, the results of our research differed slightly from those of published studies^{14, 26, 39}. These studies reported no difference in LR among patients with various tumor subtypes. We found that molecular subtype was a prognostic factor for both LR and DM, but not an independent prognostic factor based on the Cox proportional hazard model.

We found the cumulative probability of 5- and 10-year OS was 91.9% and 86.2%, respectively, in YBC patients ≤ 35 years of age in our study. A population-based study of women diagnosed with breast cancer from 1992–2005 demonstrated that the breast cancer-specific survival of patients < 35 years of age was 69% at the 10-year follow-up evaluation²⁷. Jacqueline et al.³⁸ reported that the 5-year breast cancer net survival in females diagnosed between 2001 and 2009 was 88.2% independent of race and age, and the survival rates improved from the 2001 and 2003 to 2004 and 2009. Another study suggested that the 5-year breast cancer-specific survival increased from 74.0% during 1975–1979 to 88.5% during 2010–2015 in women diagnosed between ages 20 and 39 years from the SEER database²⁰. The data obtained in our research were slightly higher than previous studies, which might be due to the recent study year accompanied by the improved treatment methods. In addition, the 10 years of follow-up data were not available for patients between 2010 and 2014. Lastly, our study might be limited by the single-center and retrospective nature. In short, the survival rate of YBC patients has improved in recent years.

Our findings demonstrated that the differences in prognosis among YBC patients varied with molecular subtype. Women with HR-/HER2+ had the worst LRFI, RRFI, DMFI, and OS compared to the other subtypes, which was consistent with previous articles^{33, 24, 29, 30}. Nevertheless, many studies have indicated that YBC patients with luminal B subtype had a worse prognosis^{27, 28, 31, 32}. The reason causing the discrepant results might be connected to the year of the study (i.e., there was no HER2-targeted therapy until 1998). After the development of HER2-targeted therapy, the survival of HER2-positive patients was greatly improved⁴⁰. With the rapid development of HER2-targeted therapies, such as the combination of trastuzumab and pertuzumab, and neratinib and T-DM1, the outcomes of HER2-positive patients could be further improved^{41–43}.

However, there were some limitations in our study. First, molecular subtypes were categorized according to HR and HER2 status without other marks, such as Ki-67, and analyses of HER2 status were limited by FISH testing that was not performed in some cases. Thus, we could not further subdivide the molecular subtypes. Second, information concerning adherence to adjuvant endocrine therapy and ovary function suppression, such as goserelin, was not available on medical records obtained through the subsequent follow-up. Therefore, the reliability of information might be affected by recall bias. Third, the median follow-up of 82 months was relatively short for YBC patients. Finally, the patients were collected in a large single center in northern China and is not population based. As a result, the experiences of patients in our study might not be generalizable to all young women with breast cancer.

In conclusion, the overall 5-year LR and RR rates with YBC patients were low and showed a decreasing trend and the proportion of early-stage breast cancer increased between 2006 and 2014. The highest LR rates and worst survival in this young population were associated with HR-/HER2 + tumors. We expect to develop more new treatments to prolong the survival time and improve the quality of life of young women with breast cancer in the near future.

Abbreviation

LR Local recurrence

RR Regional recurrence

LRR Loco-regional recurrence

YBC Young breast cancer

HR Hormone receptor

HER2 Human epidermal growth factor receptor 2

OS Overall survival

DM Distant metastasis

LRFI Local recurrence-free interval

DMFI Distant metastases-free interval

RRFI Regional recurrence-free interval

ER Estrogen receptor

NA Not arrived

Declarations

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

YL designed the study, performed the research and wrote the paper. YZ performed research and analyzed data. SL performed research and checked the data. YD helped performed research and checked the data. HL designed the study and analyzed data.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Tianjin Medical University Cancer Institution and Hospital Human Research Ethics Committee.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table I . Demographic characteristics of young patients surgically treated between January 1,2006 and December 31,2014 (n=1099)

Characteristics	No. Of Patients (%)
BC family history	
YES	113 (10.3)
NO	969 (88.2)
Unknown	17 (1.5)
Reproductive history*	
YES	827 (75.3)
NO	257 (23.4)
Unknown	15 (1.4)
Breastfeeding history	
YES	745 (67.8)
NO	337 (30.7)
Unknown	17 (1.5)
Tumor size	
T1	420 (38.2)
T2	508 (46.2)
T3	88 (8.0)
T4	16 (1.5)
Tx	67 (6.1)
Stage	
I	282(25.7)
II a	383 (34.8)
II b	159 (14.5)
III a	126 (11.5)
III b	8 (0.7)
III c	97 (8.8)
Unknown	44 (4.0)
Lymph node metastasis	
N0	585 (53.2)
N1	276(25.1)
N2	124 (11.3)
N3	94 (8.6)
Unknown	20 (1.8)
Histological grade	
Well differentiated	35(3.2)
Moderately differentiated	594(54.0)
Poorly differentiated	163(14.8)
Unknown	307(27.9)
Pathological type	

Invasive ductal carcinoma	999(90.9)
Invasive lobular carcinoma	10(0.9)
Others	90(8.2)
Final surgery	
Breast-conserving surgery	257(23.4)
Mastectomy	842(76.6)
Biomarker subtype	
HR+/HER2-	594(54.0)
HR+/HER2+	120(10.9)
HR-/HER2+	75(6.8)
HR-/HER2-	201(18.3)
Unknown	109(9.9)
Neoadjuvant chemotherapy	
YES	176(16.0)
NO	923(84.0)
Adjuvant chemotherapy regimens	
Anthracycline-based	140(12.7)
Anthracycline-and taxane-based	884(80.4)
Unknown	67(6.1)
None	8(0.7)
Radiotherapy	
YES	557(50.7)
NO	453(41.2)
Unknown	89(8.1)
Adjuvant hormonal therapy	
YES	589(53.6)
NO	316(28.8)
Unknown	194(17.7)
Ovarian fuction suppression	
YES	187(17.0)
NO	545(49.6)
Unknown	367(33.4)
Trastuzumab treatment	
YES	85(7.7)
NO	836(76.1)
Unknown	178(16.2)

Abbreviations:BC ,breast cancer HR+, hormone receptor positive; HR-, hormone receptor negative; HER2+,human epidermal growth factor 2 positive; HER2-,human epidermal growth factor 2 negative;

* reproductive history: yes means they had children.

Table II. Baseline demographic characteristics of all young patients according to the various biomarker subtypes (n=1099)

Characteristics	HR+/HER2-(n=594)	HR+/HER2+(n=120)	HR-/HER2+(n=75)	HR-/HER2-(n=201)	Unknown (n=109)	P
BC family history						0.023
YES	62(10.4)	16(13.3)	5(6.7)	21(10.4)	9(8.3)	
NO	524(88.2)	104(86.7)	68(90.7)	179(89.1)	94(86.2)	
Unknown	8(1.3)	0(0)	2(2.7)	1(0.5)	6(5.5)	
Reproductive history						0.003
YES	451(75.9)	92(76.7)	61(81.3)	146(72.6)	77(70.6)	
NO	136(22.9)	28(23.3)	12(16.0)	55(27.4)	26(23.9)	
Unknown	7(1.2)	0(0)	2(2.7)	0(0)	6(5.5)	
Breastfeeding history						<0.001
YES	410(69.0)	79(65.8)	59(78.7)	128(63.7)	69(63.3)	
NO	177(29.8)	41(34.2)	14(18.7)	72(35.8)	33(30.3)	
Unknown	7(1.2)	0(0)	2(2.7)	1(0.5)	7(6.4)	
Tumor size						0.007
T1	250(42.1)	39(32.5)	17(22.7)	69(34.3)	45(41.3)	
T2	261(43.9)	61(50.8)	40(53.3)	103(51.2)	43(39.4)	
T3	45(7.6)	10(8.3)	8(10.7)	12(6.0)	13(11.9)	
T4	3(0.5)	5(4.2)	3(4.0)	4(2.0)	1(0.9)	
Tx	35(5.9)	5(4.2)	7(9.3)	13(6.5)	7(6.4)	
Stage						<0.001
I	166(27.9)	27(22.5)	8(10.7)	48(23.9)	33(30.3)	
II a	199(33.5)	40(33.3)	26(34.7)	90(44.8)	28(25.7)	
II b	85(14.3)	16(13.3)	13(17.3)	28(13.9)	17(15.6)	
III a	72(12.1)	15(12.5)	12(16.0)	17(8.5)	10(9.2)	
III b	2(0.3)	1(0.8)	2(2.7)	3(1.5)	0(0)	
III c	48(8.1)	17(14.2)	12(6.0)	4(2.0)	16(14.7)	
Unknown	22(3.7)	4(3.3)	2(2.7)	11(5.5)	5(4.6)	
^a LN metastasis						<0.001
N0	312(52.5)	55(45.8)	36(48.0)	134(66.7)	48(44.0)	
N1	161(27.1)	30(25.0)	14(18.7)	46(22.9)	25(22.9)	
N2	70(11.8)	16(13.3)	13(17.2)	16(8.0)	9(8.3)	
N3	46(7.7)	17(14.2)	12(16.0)	2(1.0)	17(15.6)	
Unknown	5(0.8)	2(1.7)	0(0)	3(1.5)	10(9.2)	
Histological grade						<0.001
Well differentiated	29(4.9)	0(0)	1(1.3)	2(1.0)	3(2.8)	
Moderately differentiated	371(62.5)	67(55.8)	36(48.0)	78(38.8)	42(38.5)	
Poorly differentiated	50(8.4)	25(20.8)	16(21.3)	52(25.9)	20(18.3)	
Unknown	144(24.2)	28(23.3)	22(29.3)	69(34.3)	44(40.4)	
Pathological type						0.906

IDC	534(89.9)	110(91.7)	71(94.7)	183(91.0)	101(92.7)
IBC	7(1.2)	1(0.8)	0(0)	1(0.5)	1(0.9)
Others	53(8.9)	9(7.5)	4(5.3)	17(8.5)	7(6.4)
Final surgery	0.002				
BCS	143(24.1)	19(15.8)	14(18.7)	64(31.8)	17(15.6)
Mastectomy	451(75.9)	101(84.2)	61(81.3)	137(68.2)	92(84.4)
Neoadjuvant chemotherapy	0.003				
YES	80(13.5)	19(15.8)	23(30.7)	33(16.4)	21(19.3)
NO	514(86.5)	101(84.2)	52(69.3)	168(83.6)	88(80.7)
Adjuvant chemotherapy	0.046				
A-based	72(12.1)	17(14.2)	12(16.0)	24(11.9)	15(13.8)
A and T-based	490(82.5)	97(80.8)	58(77.3)	162(80.6)	77(70.6)
Unknown	28(4.7)	6(5.0)	5(6.7)	12(6.0)	16(14.7)
None	4(0.7)	0(0)	0(0)	3(1.5)	1(0.9)
Radiotherapy	<0.001				
YES	304(51.2)	59(49.2)	46(61.3)	105(52.2)	43(39.4)
NO	254(42.8)	52(43.3)	24(32.0)	85(42.3)	38(34.9)
Unknown	36(6.1)	9(7.5)	5(6.7)	11(5.5)	28(25.7)
Hormonal therapy	<0.001				
YES	467(78.6)	89(74.2)	0(0)	0(0)	33(30.3)
NO	27(4.5)	8(6.7)	70(93.3)	194(96.5)	17(15.6)
Unknown	100(16.8)	23(19.2)	5(6.7)	7(3.5)	59(54.1)
OFS	<0.001				
YES	147(24.7)	34(28.3)	0(0)	0(0)	6(5.5)
NO	215(36.2)	46(38.3)	67(89.3)	189(94.0)	28(25.7)
Unknown	232(39.1)	40(33.3)	8(10.7)	12(6.0)	75(68.8)
Trastuzumab therapy	<0.001				
YES	2(0.3)	51(42.5)	32(42.7)	0(0)	0(0)
NO	553(93.1)	41(34.2)	23(30.7)	195(97.0)	24(22.0)
Unknown	39(6.6)	28(23.3)	20(26.7)	6(3.0)	85(78.0)

NOTE. All data are given as No.of patients (%). None represents no chemotherapy has been adopted.

Abbreviations:LN,Lymph node; IDC,Invasive ductal carcinoma; IBC,Invasive lobular carcinoma; BCS, Breast-conserving surgery; A-based, Anthracycline-based; A and T-based, Anthracycline-and taxane-based; OFS,Ovarian function suppression.

Table III. Tumor Characteristics for all young breast cancer patients according to the time of diagnosis (n=1099)

Characteristics	2006 n=(55)	2007 n=(73)	2008 n=(96)	2009 n=(93)	2010 n=(132)	2011 n=(154)	2012 n=(147)	2013 n=(166)	2014 n=(183)	P
Tumor size										
T1	21(38.2)	27(37.0)	39(40.6)	37(39.8)	45(34.1)	64(41.6)	49(33.3)	62(37.3)	76(41.5)	0.539
T2	30(54.5)	34(46.6)	43(44.8)	42(45.2)	61(46.2)	65(42.2)	75(51.0)	82(49.4)	76(41.5)	
T3	2(3.6)	3(4.1)	5(5.2)	5(5.4)	16(12.1)	13(8.4)	15(10.2)	12(7.2)	17(9.3)	
T4	1(1.8)	2(2.7)	3(3.1)	0(0.0)	1(0.8)	1(0.6)	4(2.7)	2(1.2)	2(1.1)	
Tx	1(1.8)	7(9.6)	6(6.3)	9(9.7)	9(6.8)	11(7.1)	4(2.7)	8(4.8)	12(6.6)	
Stage										0.004
I	11(20.0)	21(28.8)	27(28.1)	24(25.8)	30(22.7)	40(26.0)	35(23.8)	45(27.1)	49(26.8)	
II a	24(43.6)	20(27.4)	37(38.5)	36(38.7)	41(31.1)	47(30.5)	56(38.1)	51(30.7)	71(38.8)	
II b	4(7.3)	11(15.1)	9(9.4)	13(14.0)	17(12.9)	19(12.3)	27(18.4)	36(21.7)	23(12.6)	
III a	13(23.0)	7(9.6)	8(8.3)	8(8.6)	22(16.7)	20(13.0)	13(8.8)	14(8.4)	21(11.5)	
III b	0(0.0)	2(2.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(1.4)	2(1.2)	2(1.1)	
III c	3(5.5)	5(6.8)	14(14.6)	4(4.3)	14(10.6)	21(13.6)	12(8.2)	13(7.8)	11(6.0)	
Unknown	0(0.0)	7(9.6)	1(1.0)	8(8.6)	8(6.1)	7(4.5)	2(1.4)	5(3.0)	6(3.3)	
Lymph node metastasis										0.007
N0	30(54.5)	42(57.5)	56(58.3)	52(55.9)	67(50.8)	73(47.4)	80(54.4)	83(50.0)	102(55.7)	
N1	8(14.5)	15(20.5)	19(19.8)	26(28.0)	30(22.7)	38(24.7)	41(27.9)	54(32.5)	45(24.6)	
N2	13(23.6)	11(15.1)	6(6.3)	10(10.8)	19(14.4)	20(13.0)	12(8.2)	15(9.0)	18(9.8)	
N3	4(7.3)	5(6.8)	14(14.6)	5(5.4)	14(10.6)	21(13.6)	11(7.5)	11(6.6)	9(4.9)	
Unknown	0(0.0)	0(0.0)	1(1.0)	0(0.0)	2(1.5)	2(1.3)	3(2.0)	3(1.8)	9(4.9)	
Histological grade										0.415
Well differentiated	4(7.3)	2(2.7)	6(6.3)	3(3.2)	4(3.0)	8(5.2)	3(2.0)	3(1.8)	2(1.1)	
Moderately differentiated	32(58.2)	35(47.9)	47(49.0)	53(57.0)	76(57.6)	84(54.5)	86(58.5)	87(52.4)	94(51.4)	
Poorly differentiated	6(10.9)	10(13.7)	11(11.5)	10(10.8)	16(12.1)	26(16.9)	23(15.6)	29(17.5)	32(17.5)	
Unknown	13(23.6)	26(35.6)	32(33.3)	27(29.0)	36(27.3)	36(23.4)	35(23.8)	47(28.3)	55(30.1)	
Pathological type										0.620
Invasive ductal carcinoma	48(87.3)	68(93.2)	80(83.3)	86(92.5)	119(90.2)	140(90.0)	136(92.5)	153(92.2)	169(92.3)	
Invasive lobular carcinoma	0(0.0)	1(1.4)	1(1.0)	1(1.1)	2(1.5)	2(1.3)	0(0.0)	1(0.6)	2(1.1)	
Others	7(12.7)	4(5.5)	15(15.6)	6(6.5)	12(7.8)	12(7.8)	11(7.5)	12(7.2)	12(6.6)	
Biomarker subtype										0.043
HR+/HER2-	32(58.2)	49(67.1)	51(53.1)	50(53.8)	68(51.5)	90(58.4)	72(49.0)	89(53.6)	93(50.8)	
HR+/HER2+	9(16.4)	9(12.3)	7(7.3)	5(5.4)	9(6.8)	21(13.6)	15(10.2)	22(13.3)	23(12.6)	

HR-/HER2+	3(5.5)	6(8.2)	6(6.3)	5(5.4)	12(9.1)	13(8.4)	12(8.2)	11(6.6)	7(3.8)
HR-/HER2-	8(14.5)	6(8.2)	20(20.8)	26(28.0)	33(25.0)	16(10.4)	28(19.0)	27(16.3)	37(20.2)
Unknown	3(5.5)	3(4.1)	12(12.5)	7(7.5)	10(7.6)	14(9.1)	20(13.6)	17(10.2)	23(12.6)

Table IV. 5 year of Local, Regional and distant recurrence rates of young breast cancer patients treated between 2006 to 2014 (n=1099)

Year	No.of patients	LR,No.(%)	P	RR,No.(%)	P	DM,No.(%)	P
Overall	1099	69(6.7)		52(5.1)		176(16.6)	
2006	55	7(13.0)	0.028	4(7.4)	0.015	10(18.2)	0.228
2007	73	5(7.3)		10(14.4)		14(19.4)	
2008	96	12(13)		9(9.8)		17(18.3)	
2009	93	4(4.5)		3(3.3)		16(17.2)	
2010	132	7(5.6)		9(7.1)		17(13.1)	
2011	154	12(8.2)		7(4.7)		32(21.3)	
2012	147	8(6.1)		2(1.5)		25(17.6)	
2013	166	8(4.9)		5(3.2)		20(12.3)	
2014	182	6(3.4)		3(1.7)		25(15.8)	

Table V. Cox proportional hazards regression model analysis of Local, Regional and distant recurrence of young breast cancer patients (n=1099)

Characteristic	LR				RR				DM			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	analysis		analysis		analysis		analysis		analysis		analysis	
	HR	P	HR	P	HR	P	HR	P	HR	P	HR	P
Tumor size	<0.01		<0.01		<0.01		0.05		<0.01		0.13	
T1	Reference		Reference		Reference		Reference		Reference		Reference	
T2	0.8(0.5-	0.40	0.5(0.2-	0.08	0.9(0.5-	0.85	0.6(0.3-	0.29	1.9(1.3-	<0.01	0.7(0.3-	0.48
	1.3)		1.1)		1.7)		1.5)		2.7)		1.7)	
T3	2.2(1.1-	0.02	1.9(0.7-	0.23	3.4(1.6-	<0.01	1.3(0.5-	0.60	5.7(3.7-	<0.01	1.5(0.6-	0.41
	4.5)		5.7)		7.0		3.2)		8.7)		3.8)	
T4	8.5(3.3-	<0.01	5.0(0.9-	0.07	9.2(3.1-	<0.01	5.6(1.4-	0.01	13.7(7.1-	<0.01	4.4(1.1-	0.04
	22.0)		27.5)		27.0)		22.5)		26.5)		18.4)	
Stage	<0.01		0.15		<0.01		0.10		<0.01		0.07	
I	Reference		Reference		Reference		Reference		Reference		Reference	
II a	1.5(0.8-	0.22	1.8(0.7-	0.20	0.4(0.2-	0.09	0.5(0.1-	0.26	2.1(1.2-	<0.01	0.5(0.1-	0.18
	2.9)		4.5)		1.1)		1.6)		3.5)		1.4)	
II b	2.0(1.0-	0.06	2.2(0.6-	0.26	2.0(0.9-	0.08	2.2(0.6-	0.26	3.4(1.9-	<0.01	1.9(0.5-	0.38
	4.3)		8.5)		4.5)		9.0)		6.0)		7.9)	
III a	1.0(0.4-	0.92	0.7(0.1-	0.66	3.6(1.7-	<0.01	0.9(0.2-	0.89	6.2(3.6-	<0.01	0.6(0.1-	0.60
	2.7)		3.5)		7.5)		4.5)		10.6)		3.4)	
III b	7.8(1.8-	<0.01	1.5(0.2-	0.73	4.3(0.6-	0.16	0.4(0.0-	0.46	14.8(5.5-	<0.01	0.5(0.0-	0.56
	34.3)		14.4)		33.1)		5.3)		39.6)		6.5)	
III c	3.8(1.5-	<0.01	0.4(0.0-	0.32	4.1(1.8-	<0.01	0.2(0.0-	0.12	12.9(7.6-	<0.01	0.1(0.0-	0.48
	9.5)		2.6)		9.1)		1.6)		21.8)		1.0)	
LN metastasis	<0.01		0.03		<0.01		0.02		<0.01		<0.01	
N0	Reference		Reference		Reference		Reference		Reference		Reference	
N1	2.3(1.4-	<0.01	1.9(1.0-	0.07	2.3(1.1-	0.02	1.6(0.6-	0.31	2.1(1.5-	<0.01	2.0(0.7-	0.17
	3.7)		3.9)		4.6)		4.3)		3.0)		5.2)	
N2	1.0(0.4-	0.95	1.0(0.3-	0.98	5.9(3.0-	<0.01	7.1(1.7-	<0.01	3.8(2.6-	<0.01	12.0(2.6-	<0.01
	2.3)		3.4)		11.5)		30.2)		5.6)		56.2)	
N3	3.9(2.1-	<0.01	9.6(1.8-	<0.01	6.9(3.3-	<0.01	30.0(3.5-	<0.01	8.1(5.6-	<0.01	78.3(6.8-	<0.01
	7.3)		50.0)		14.5)		257.2)		11.8)		899.5)	
Histological grade	0.09		-		0.81		-		0.21		-	
I	Reference		-		Reference		-		Reference		-	
II	0.6(0.2-	0.26	-		0.7(0.2-	0.60	-		1.9(0.7-	0.19	-	
	1.6)				2.4)				5.3)			
III	1.1(0.4-	0.86	-		1.0(0.3-	0.97	-		2.5(0.9-	0.08	-	
	3.3)				3.5)				7.0)			
Final surgery	0.14		-		0.30		-		<0.01		0.10	
Mastectomy	Reference		-		Reference		-		Reference		Reference	

BCS	1.4(0.9- 0.13 2.3)	-	0.7(0.4- 0.30 1.3)	-	0.4(0.3- <0.01 0.7)	1.9(0.9- 0.06 4.2)
ER status	<0.01	0.46	0.16	-	0.35	-
Positive	Reference	Reference	Reference	-	Reference	-
Negative	2.0(1.3- <0.01 3.1)	1.8(0.7- 0.23 4.6)	1.6(1.0- 0.06 2.7)	-	1.2(0.9- 0.25 1.6)	-
PR status	<0.01	0.44	0.94	-	0.93	-
Positive	Reference	Reference	Reference	-	Reference	-
Negative	1.9(1.2- <0.01 2.9)	1.6(0.6- 0.33 3.9)	1.1(0.7- 0.72 1.9)	-	1.1(0.8- 0.71 1.4)	-
HER2 status	<0.01	0.34	0.59	-	<0.01	0.95
Positive	Reference	Reference	Reference	-	Reference	Reference
Negative	0.5(0.3- <0.01 0.8)	0.0(0.0- 0.94 NA)	0.8(0.4- 0.38 1.4)	-	0.6(0.4- <0.01 0.8)	0.0(0.0- 0.94 NA)
Biomarker subtype	<0.01	0.31	0.66	-	<0.01	0.05
HR+/HER2-	Reference	Reference	Reference	-	Reference	Reference
HR+/HER2+	1.7(0.8- 0.15 3.4)	0.0(0.0- 0.94 NA)	1.0(0.4- 0.94 2.3)	-	1.5(1.0- 0.06 2.2)	0.0(0.0- 0.94 NA)
HR-/HER2+	3.5(1.8- <0.01 6.7)	0.0(0.0- 0.93 NA)	1.7(0.8- 0.18 3.9)	-	1.9(1.2- <0.01 2.9)	0.0(0.0- 0.96 NA)
HR-/HER2-	1.5(0.8- 0.20 2.7)	0.3(0.1- 0.06 1.1)	0.9(0.4- 0.73 1.8)	-	0.7(0.5- 0.15 1.1)	2.6(1.1- 0.04 6.4)
Adjuvant chemotherapy	0.18	-	0.70	-	0.29	-
A and T-based	Reference	-	Reference	-	Reference	-
A-based	1.2(0.7- 0.47 2.2)	-	1.3(0.7- 0.48 2.5)	-	1.2(0.8- 0.42 1.7)	-
Radiotherapy	0.20	-	0.03	0.16	<0.01	0.03
NO	Reference	-	Reference	Reference	Reference	Reference
YES	1.1(0.7- 0.56 1.8)	-	1.9(1.1- 0.03 3.3)	0.6(0.3- 0.14 1.2)	2.5(1.8- <0.01 3.5)	0.3(0.1- 0.02 0.8)
Trastuzumab therapy	<0.01	0.01	0.09	-	0.22	-
NO	Reference	Reference	Reference	-	Reference	-
YES	0.5(0.3- <0.01 0.7)	0.4(0.2- 0.05 1.0)	0.7(0.4- 0.30 1.3)	-	1.1(0.8- 0.71 1.5)	-
OFS	0.52	-	<0.01	0.02	<0.01	<0.01
NO	Reference	-	Reference	Reference	Reference	Reference
YES	1.2(0.6- 0.64 2.1)	-	3.4(1.8- <0.01 6.2)	2.4(1.3- <0.01 4.7)	3.7(2.6- <0.01 5.3)	5.0(2.1- <0.01 11.7)
Trastuzumab therapy	<0.01	<0.01	0.16	-	<0.01	0.55

NO	Reference	Reference	Reference	-	Reference	Reference
YES	1.5(0.7- 0.31 3.3)	1.1(0.4- 0.79 3.1)	0.9(0.3- 0.90 2.6)	-	1.4(0.9- 0.14 2.3)	0.6(0.2- 0.37 2.0)
Unknown	2.8(1.8- <0.01 4.6)	3.3(1.6- <0.01 6.7)	1.7(1.0- 0.06 3.1)	-	1.9(1.3- <0.01 2.6)	1.1(0.5- 0.78 2.8)

Table VI. Relapse and survival of outcomes in young breast cancer patients according to various molecular subtypes

outcome	5-Year			10-Year		
	5-Year Estimate (%)	95%CI	Total Number of Events	10-Year Estimate (%)	95%CI	Total Number of Events
Overall						
LRFI	93.3	91.6 to 94.7	61	90.4	87.9 to 92.5	71
RRFI	95.0	93.4 to 96.1	47	92.4	90.1 to 94.2	57
DMFI	83.5	81.1 to 85.6	155	78.3	75.4 to 80.9	186
OS	91.9	90.1 to 93.4	76	86.2	83.2 to 88.7	101
HR+/HER-						
LRFI	95.6	94.0 to 97.0	25	92.7	89.0 to 95.1	32
RRFI	95.5	93.4 to 97.0	25	91.9	88.3 to 94.5	34
DMFI	85.6	82.4 to 88.2	83	78.5	74.4 to 82.1	107
OS	94.3	92.0 to 95.9	32	87.6	83.2 to 91.0	49
HR+/HER+						
LRFI	90.7	83.4 to 94.9	10	90.7	83.4 to 94.9	10
RRFI	94.5	88.0 to 97.5	6	94.5	88.1 to 97.5	6
DMFI	77.1	68.1 to 83.8	26	73.4	63.9 to 80.8	29
OS	87.3	79.5 to 92.3	14	80.3	68.1 to 88.3	17
HR-/HER+						
LRFI	83.1	72.0 to 90.0	12	81.3	69.9 to 88.8	13
RRFI	91.8	82.7 to 96.3	6	90.0	80.0 to 95.1	7
DMFI	71.7	59.9 to 80.5	20	68.6	56.6 to 77.9	23
OS	77.9	66.5 to 85.8	16	71.4	56.8 to 81.8	18
HR-/HER2-						
LRFI	92.5	87.6 to 95.5	14	90.6	84.7 to 94.3	16
RRFI	94.7	90.4 to 97.1	10	94.7	90.4 to 97.1	10
DMFI	86.7	81.1 to 90.8	26	86.1	80.3 to 90.2	27
OS	92.7	88.0 to 95.6	14	89.9	83.8 to 93.8	17

Figures

Figure 1

Local(A), Regional(B) and Distant metastases(C) rates of young breast cancer patients treated between 2006 to 2014 according to various biomarker subtypes (n=1099)

Figure 2

Overall survival of young patients with breast cancer according to various molecular subtypes

Number at risk

HR+/HER2-	594	514	168	12
HR+/HER2+	120	93	19	3
HR-/HER2+	75	54	20	0
HR-/HER2-	201	164	63	2
Unknown	109	81	22	2

Figure 3

Nelson-Aalen cumulative hazard estimates for Local recurrence-free interval for all young patients by molecular subtypes

Nelson-Aalen cumulative hazard estimates

Number at risk

HR+/HER2-	594	484	166	12
HR+/HER2+	120	89	20	3
HR-/HER2+	75	55	19	0
HR-/HER2-	201	165	67	2
Unknown	109	76	21	2

Figure 4

Nelson-Aalen cumulative hazard estimates for distant metastases-free interval for all young patients by molecular subtypes