RESEARCH ARTICLE

# HER2-enriched Tumors Have the Highest Risk of Local Recurrence in Chinese Patients Treated with Breast Conservation Therapy

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## Abstract

**Purpose: The purpose of this study was to investigate the recurrence pattern and characteristics of patients based on the 2013 St. Gallen surrogate molecular subtypes after breast-conserving surgery (BCS) in Chinese women. Methods: This retrospective analysis included 709 consecutive breast cancer patients undergoing BCS from 1999-2010 at our institution. Five different surrogate subtypes were created using combined expression of the estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2. Locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS) rates were calculated. Results: The 5-year LRRFS, DMFS, and DFS rates were 90.5%, 88.2%, and 81.5%, respectively. Multivariate analysis revealed that young age, node-positive disease, and HER2 enrichment were independent prognostic factors in LRRFS patients. There was also an independent prognostic role of lymph node-positive disease in DMFS and DFS patients. Patients with luminal A tumors had the most favorable prognosis, with LRRFS, DMFS, and DFS rates of 93.2%, 91.5%, and 87.4% at 5 years, respectively. Conversely, HER-2-enriched tumors exhibited the highest rate of locoregional recurrence (20.6%). Conclusion: Surrogate subtypes present with significant differences in RFS, DMFS, and LRRFS. Luminal A tumors have the best prognosis, whereas HER2-enriched tumors have the poorest.**

**Keywords:** Breast cancer - recurrence - molecular subtype - breast-conserving surgery

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## Introduction

Breast-conserving surgery (BCS) with radiation therapy is now well established as a standard treatment option for women with early-stage invasive breast cancers. Multiple prospective, randomized trials have demonstrated equivalent survival between patients treated with BCS and mastectomy (Veronesi et al., 2002), although BCS is associated with a higher risk for local recurrence than mastectomy (Veronesi et al., 2002).

The use of BCS has begun to increase in China over recent decades. Nonetheless, only 5.5-9% of women undergo BCS (Li et al., 2011), and the risk of local recurrence after BCS is a major concern.

Clinical and pathologic risk factors are important for estimating the local recurrence risk after BCS. The traditional well-defined risk factors include margin status after resection, young age, axillary lymph node involvement, tumor size, and histologic grade (Leij et al., 2012). Molecular subtypes have also recently been demonstrated to identify patients at increased risk of local recurrence (Voduc et al., 2010).

The 2011 St. Gallen consensus meeting recently advised the use of four biomarkers (estrogen receptor (ER), progesterone receptor (PR), HER-2, and Ki67) as a surrogate of intrinsic subtype classification (Goldhirsch et al., 2011). As a diagnostic test is not yet routinely available for Ki67, the 2013 St. Gallen consensus proposed the use of the PR level instead of Ki67.

However, breast cancer is a heterogeneous disease, and the biological features of breast cancer among Chinese women are somewhat different from those among western women. The differences include a younger patient age in China, where more than half of breast cancer patients are premenopausal (Fan et al., 2009). Of note, very few studies examining the outcomes of BCS in a Chinese population have been reported. There is a need to understand the characteristics of local recurrence and metastasis after BCS in Chinese women with early-stage breast cancer. This study retrospectively analyzed risk factors and prognostic factors for local recurrence and recurrence-free survival (RFS), including age and body mass index as well as the 2013 St. Gallen panel of prognostic markers, in Chinese women who underwent BCS.

## Materials and Methods

From November 1999 to July 2010, 2,134 breast cancer

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**Table 1. Descriptive Analysis and Outcomes for the Five Phenotypes**

| N, % | Luminal A | Luminal B1 | Luminal B2 | HER2- enriched | Basal-like | Total | *P* value |
|---|---|---|---|---|---|---|---|
| All | 290 (40.9) | 124 (17.5) | 72 (10.2) | 76 (10.7) | 147 (20.7) | 709 (100) | |
| Age (yr) | | | | | | | 0.327 |
| <=40 | 78 (26.9) | 34 (27.4) | 25 (34.7) | 23 (30.3) | 32 (21.8) | 192 (27.1) | |
| >40 | 212 (73.1) | 90 (72.6) | 47 (65.3) | 53 (69.7) | 115 (78.2) | 517 (72.9) | |
| Tumor stage | | | | | | | 0.068 |
| pT1 | 212 (75.4) | 78 (66.1) | 47 (67.1) | 45 (60.0) | 98 (71.0) | 480 (70.4) | |
| pT2 | 69 (24.6) | 40 (33.9) | 23 (32.9) | 30 (40.0) | 40 (29.0) | 202 (29.6) | |
| Node stage | | | | | | | 0.12 |
| 0 | 200 (69.0) | 86 (69.4) | 48 (66.7) | 40 (52.6) | 107 (72.8) | 481 (67.8) | |
| 1 | 66 (22.8) | 30 (24.2) | 15 (20.8) | 22 (28.9) | 29 (19.7) | 162 (22.8) | |
| 2 | 20 (6.9) | 7 (5.6) | 6 (8.3) | 10 (13.2) | 6 (4.1) | 49 (6.9) | |
| 3 | 4 (1.4) | 1 (0.8) | 3 (4.2) | 4 (5.3) | 5 (3.4) | 17 (2.4) | |
| Grade | | | | | | | <0.001 |
| 1 | 54 (18.9) | 10 (8.2) | 8 (11.1) | 11 (14.7) | 5 (3.5) | 88 (12.6) | |
| 2 | 182 (63.6) | 76 (62.3) | 31 (43.1) | 31 (41.3) | 77 (53.5) | 397 (56.8) | |
| 3 | 500 (17.5) | 36 (29.5) | 33 (45.8) | 33 (44.0) | 62 (43.1) | 214 (30.6) | |
| Chemotherapy | | | | | | | 0.004 |
| Neoadjuvant | 34 (11.7) | 16 (12.9) | 16 (22.2) | 21 (27.6) | 27 (18.4) | 114 (16.1) | |
| BMI | | | | | | | 0.727 |
| <=18 | 15 (5.5) | 6 (5.9) | 9 (13.6) | 2(2.7) | 6 (4.4) | 38 (5.8) | |
| 18~ | 199 (72.9) | 75 (73.5) | 43 (65.2) | 55 (74.3) | 98 (72.6) | 470 (72.3) | |
| 25~ | 50 (18.3) | 19 (18.6) | 12 (18.2) | 15 (20.3) | 28 (20.7) | 124 (19.1) | |
| >=30 | 9 (3.3) | 2 (2.0) | 2 (3.0) | 2 (2.7) | 3 (2.2) | 18 (2.8) | |
| LRRFS(%)(95%CI) | 93.2(88.5~98.0) | 91.8 (84.4~99.2) | 88.0 (79.7~96.4) | 79.4 (62.2~96.5) | 91.6 (86.4~96.7) | 90.5(84.7~91.8) | 0.016 |
| DMFS(%) (95%CI) | 91.5 (85.6~97.4) | 89.1 (81.7~96.6) | 81.9 (69.5~94.4) | 77.1 (63.7~90.6) | 90.6 (85.3~95.8) | 88.2 (84.7~91.8) | 0.002 |
| DFS(%) (95%CI) | 87.4 (80.8~94.1) | 82.6 (73.4~91.9) | 74.8 (61.3~88.3) | 65.5 (49.1~81.9) | 81.7 (73.3~90.1) | 81.5 (77.2~85.8) | 0.001 |

patients underwent mastectomy or lumpectomy at Sun Yat-sen Memorial Hospital. This study retrospectively reviewed 750 patients who underwent BCS. Patient characteristics, medical comorbidities, tumor location, surgical details, postoperative outcome, and follow-up status were collected prospectively and recorded in a breast cancer database. Forty-one patients were excluded because of ductal carcinoma in situ. Thus, 709 patients were included in this study.

The patients consented to the chosen surgical procedures. Selection for BCS was dependent on patient acceptance, tumor characteristics, and the surgeon's preference. Multicentricity and tumors larger than 3 cm are generally considered contraindications to BCS in our practice. The BCS technique was performed as described previously (Chen et al., 2012; Yang et al., 2012). Patients receiving breast conservation underwent a sentinel lymph node biopsy or a level I or II axillary lymph node dissection. Radiotherapy was administered to all the BCS patients at a median dose of 50 Gy to the whole breast, typically in fractions of 2 Gy. Boost doses were administered at the primary tumor site. A separate supraclavicular or axillary field was not typically added after axillary dissection unless the patient had four or more positive nodes. The patients received systemic adjuvant chemotherapy according to the St. Gallen and/or National comprehensive cancer network (NCCN) guidelines. None of the patients received trastuzumab as adjuvant therapy. The standard adjuvant hormone therapy was added for patients with hormone receptor-positive breast cancer according to the above guidelines.

ER, PR, and HER-2 analyses were performed using immunohistochemical (IHC) staining techniques. Tumors with greater than 1% of total tumor cells staining for ER or PR of any intensity were considered positive. Tumors with more than 10% PR-positive cells were considered high PR. The HER-2 staining intensity score was evaluated relative to the provided control slides from 0 to 3+, and specimens staining 3+ were coded as positive. The patients were categorized based on IHC of their tumor in the following manner: luminal A (ER+ and/or PR+, HER-2-, and PR high); luminal B1 (ER+ and/or PR+, HER-2-, and PR low); luminal B2 (ER+ and/or PR+ and HER-2+); HER2 enriched (ER-, PR-, and HER-2+); and basal-like (ER-, PR-, and HER-2-). The body mass index (BMI) of each patient was calculated using the following formula: weight (kg)/height$^2$ (m$^2$). BMI was analyzed as a categorical variable. A low BMI was defined as <18 kg/m$^2$, a normal BMI as 18-24 kg/m$^2$, and a high BMI as 25-29 kg/m$^2$. An obese BMI was considered ≥30 kg/m$^2$.

**Table 2. Recurrence Events During Follow-up**

| Recurrence event | Number | Incidence (%) |
|---|---|---|
| Distant metastasis | 53 | 7.5 |
| Locoregional recurrence | 40 | 5.7 |
| Ipsilateral breast | 27 | 3.8 |
| Contralateral breast cancer | 8 | 1.1 |
| Secondary cancer | 3 | 0.4 |

We evaluated the rates of locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS). For locoregional recurrence-free survival, the duration of follow-up was calculated from the date of BCS to the date of local recurrence (including relapse in the chest wall, local skin, surgical scar, or ipsilateral breast as well as recurrence in the internal mammary, supraclavicular, and ipsilateral axillary nodes). DMFS is defined as the interval between diagnosis and the recurrence of any distant disease. Disease-free survival was calculated from the date of BCS to the date of local recurrence, distant metastasis,

**Table 3. Univariate Survival Analysis for LRRFS, DFS, and DMFS after BCS**

| Variable | LRRFS | | DMFS | | DFS | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95%CI) | *P* Value | HR (95%CI) | *P* Value |
| Age (yr)>=40(vs<40 ) | 0.38 (0.21-0.71) | 0.002 | 0.53 (0.31-0.92) | 0.024 | 0.54 (0.35-0.84) | 0.007 |
| Tumor stage T2(vs T1) | 2.16 (1.14-4.10) | 0.018 | 1.32 (0.75-2.32) | 0.344 | 1.77 (1.12-2.80) | 0.014 |
| Node Positive(vs negative) | 2.48(1.33-4.63) | 0.004 | 2.67 (1.55-4.58) | <0.001 | 1.95 (1.26-3.01) | 0.003 |
| Grade 2 (vs G1) | 3.49 (0.84-14.45) | 0.085 | 5.31 (0.72-39.07) | 0.101 | 4.00 (0.97-16.53) | 0.056 |
| Grade 3 (vs G1) | 7.48 (1.80-31.10) | 0.006 | 10.35 (1.40-76.51) | 0.022 | 8.04 (1.94-33.40) | 0.004 |
| BMI<=18(vs 18~) | 2.12 (0.74-6.07) | 0.163 | 1.73 (0.68-4.41) | 0.249 | 2.60 (1.32-5.11) | 0.006 |
| BMI 25~(vs 18~) | 1.13 (0.49-2.61) | 0.773 | 0.87 (0.41-1.87) | 0.722 | 1.12 (0.62-2.03) | 0.698 |
| BMI >=30(vs 18~) | 3.07 (0.93-10.15) | 0.066 | 1.39 (0.34-5.78) | 0.649 | 2.55 (1.02-6.38) | 0.046 |
| ER Positive (vs negative) | 0.50 (0.27-0.94) | 0.032 | 0.57 (0.33-0.98) | 0.043 | 0.57 (0.37-0.89) | 0.014 |
| PR Positive (vs negative) | 0.49 (0.26-0.92) | 0.027 | 0.46 (0.27-0.79) | 0.005 | 0.45 (0.29-0.69) | <0.001 |
| HER2 Positive(vs negative) | 2.42 (1.28-4.59) | 0.007 | 2.91 (1.69-5.04) | <0.001 | 2.55 (1.63-3.99) | <0.001 |

**Table 4. Multivariate Survival Analysis of LRRFS, DFS, and DMFS after BCS**

| Variable | LRRFS | | DMFS | | DFS | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95%CI) | *P* Value | HR (95%CI) | *P* Value |
| Age (yr)>=40 (vs <40) | 0.44 (0.22-0.89) | 0.022 | 0.62 (0.34-1.12) | 0.114 | 0.69 (0.41-1.15) | 0.15 |
| Tumor stage T2 (vs T1) | 1.62 (0.83-3.17) | 0.16 | 1.07 (0.59-1.94) | 0.819 | 1.43 (0.88-2.32) | 0.145 |
| Node Positive (vs negative) | 2.16 (1.10-4.19) | 0.024 | 2.22 (1.26-3.91) | 0.006 | 1.67 (1.05-2.66) | 0.031 |
| BMI <=18 (vs 18~) | 1.09 (0.31-3.79) | 0.891 | 1.43 (0.54-3.80) | 0.472 | 2.09 (0.99-4.42) | 0.054 |
| BMI 25~ (vs 18~) | 1.37 (0.56-3.36) | 0.49 | 0.91 (0.41-2.02) | 0.823 | 1.15 (0.60-2.19) | 0.673 |
| BMI >=30 (vs 18~) | 2.99 (0.85-10.50) | 0.088 | 1.37 (0.32-5.82) | 0.671 | 2.53 (0.98-6.54) | 0.055 |
| Luminal B1 (vs Luminal A) | 1.36 (0.45-4.09) | 0.588 | 2.14 (0.86-5.31) | 0.102 | 2.16 (1.03-4.51) | 0.041 |
| Luminal B2 (vs Luminal A) | 2.73 (0.99-7.52) | 0.053 | 3.21 (1.28-8.08) | 0.013 | 2.94 (1.37-6.29) | 0.006 |
| HER2-enriched (vsLuminal A) | 2.97 (1.13-7.84) | 0.028 | 4.09 (1.75-9.59) | 0.001 | 4.17 (2.06-8.44) | <0.001 |
| Basal-like (vs Luminal A) | 2.54 (0.99-6.51) | 0.051 | 2.71 (1.16-6.32) | 0.021 | 2.56 (1.27-5.17) | 0.009 |

contralateral breast cancer, other secondary primary cancers, death, or last follow-up for patients with no recurrence. The study subjects were followed up until July 2012, and the median follow-up time was 62.5 months (range:2.6-151.7 months). Follow-up visits were conducted every 3 months during the first 2-3 years after surgery and then every 6 months after the second or third year.

Associations with LRRFS, DMFS, and DFS after BCS were evaluated using univariate and multivariate Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals (CIs). Further analyses characterized how the 2013 St. Gallen panel prognostic markers influenced LRRFS, DMFS, and DFS using Kaplan-Meier analysis. All tests were two sided, and $p$-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL).

## Results

A surrogate molecular subtype was successfully identified for 709 patients. The significant differences between the five subtypes in demographic characteristics and clinicopathological features are summarized in Table 1. We observed smaller tumor sizes for luminal B1 subtype tumors than luminal A subtype tumors. However, the luminal B1 and luminal A subtypes demonstrated similar rates of lymph node metastasis, and age and BMI did not significantly differ between these subtypes ($p$=0.327 and $p$=0.727, respectively).

The 5-year overall survival (OS), DFS, DMFS, and LRRFS rates were 95.2%, 81.5%, 88.2%, and 90.5% respectively, for all 709 patients. We observed 40 locoregional recurrences and 53 metastases. The details of the relapse events are shown in Table 2.

*Univariate and multivariate survival analyses*

The univariate analysis of potential risk factors for LRRFS, DFS, and DMFS is shown in Table 3. The results of the univariate analysis indicated that age, tumor size, node status, grade, ER status, PR status, and HER-2 status had prognostic value for LRRFS. However, young age, positive lymph node disease, higher grade (grade III), ER-negative status, PR-negative status, and HER2-positive status were risk factors for DMFS. Additionally, the following were risk factors for DFS: young age, tumor size, positive lymph node, higher grade (grade III), high or low BMI, ER-negative status, and PR-negative status. A multivariate Cox model revealed independent prognostic roles for age, node status, and HER2 enrichment in LRRFS (Table 4). In DMFS and DFS, independent prognostic roles were identified for lymph node-positive disease and the luminal B2, HER2-enriched, and basal-like subtypes. However, the luminal B1 subtype was not an independent prognostic factor for DMFS.

*Survival analysis using the 2013 St. Gallen surrogate molecular classification*

Kaplan-Meier survival analysis of patients treated with BCS revealed statistically significant differences in LRRFS (Figure 1A), DMFS (Figure 1B), and DFS (Figure

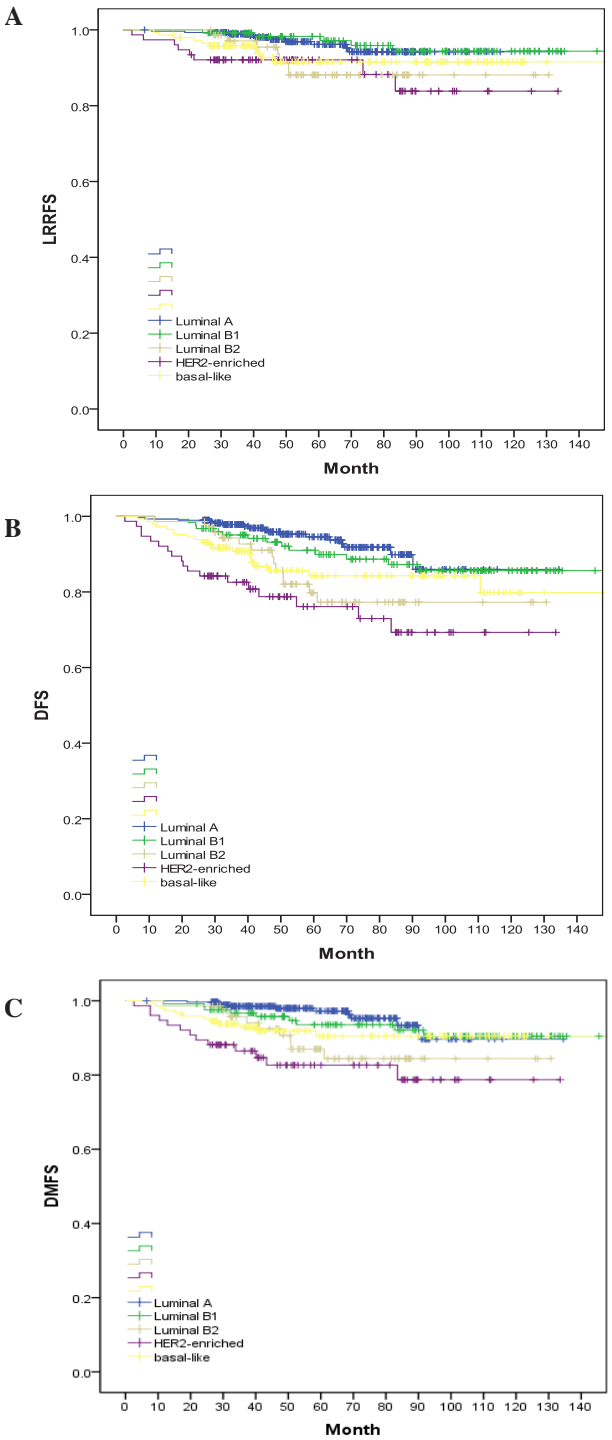


**Figure 1. Kaplan-Meier Analysis of RFS, LRRFS, and DMFS for the Five Surrogate Subtypes**

1C) among the surrogate molecular breast cancer subtypes. Patients with luminal A tumors had the most favorable prognosis, with 5-year DFS, LRRFS, and DMFS rates of 87.4%, 93.2%, and 91.5%, respectively. Conversely, the HER-2-enriched groups exhibited the highest rate of recurrence (34.5%), and the highest rate of locoregional recurrence (20.6%) (Table 1).

During the follow-up period, locoregional recurrence occurred less frequently for luminal A tumors (Table 1, Figure 1B). Luminal A tumors presented significantly better DFS when compared with the four other subtypes. HER-2-enriched tumors had the highest incidence of locoregional relapse. Additionally, the HER-2-enriched and luminal B2 subtypes had more failure events than the luminal A subtype. The luminal B1 and basal-like subtypes demonstrated intermediate outcomes (Table 1).

## Discussion

BCS is now a standard treatment for early breast cancer. In the USA, more than half of patients with early breast cancer undergo BCS (Bland et al., 1998), yet in China, BCS is performed in less than 10% of patients with breast cancer (Li et al., 2011; Li et al., 2011) due to concern for local relapse.

In our study, local relapse occurred in 40 patients (5.7%), which is similar to other studies that have reported a 5-15% rate of local recurrence (Fisher et al., 1995; Clark et al., 1996; Forrest et al., 1996; Renton et al., 1996). However, this result is slightly greater than other Asian series (2.5-4%) (Kim et al., 2005; Yau et al., 2007; Li et al., 2011). Shuang Li et al. reported a retrospective analysis that included 764 consecutive invasive breast cancer patients treated with BCS in China; their 5-year locoregional recurrence rate was 3.9%, but they also reported a safe margin of more than 5 mm (Li et al., 2011). Unfortunately, we could not investigate the effects of margin size on recurrence in the present study due to the use of the BCS technique. Racial differences could also explain the low locoregional recurrence rate (L. et al., 1997). Conversely, a surgeon's preference for more radical excision in their practice could also have resulted in a favorable outcome.

Previous studies have reported that young age, although defined by various cutoffs, is associated with increased risk of local relapse in patients undergoing BCS (Jones et al., 2009; Kim et al., 2011; Miles et al., 2012). In this retrospective study, young women (<=40 years) demonstrated a 5-year cumulative local recurrence rate of 7.8%. In a univariate analysis, young women were nearly twice as likely to experience local recurrence after BCS compared to patients older than 40 years old. A subset analysis of the EORTC trial reported that young age (<50 years) and high-grade invasive ductal carcinoma were the most important prognostic factors in determining the risk of local failure (Jones et al., 2009). In a retrospective study of 3,064 patients treated for breast cancer with BCS, Miles RC et al. found that younger age was a risk factor for local relapse. They reported that local recurrence-free survival was significantly different between women younger than 40 years and those aged 40 years and older ($p$=0.01). However, their study was limited in that it included a small sample size of only 175 patients younger than 40 years of age (Miles et al., 2012). Our results compare favorably with those reported by Hee Jeong Kim et al., who evaluated 2,102 breast cancer patients who underwent BCS at two Korean institutions. They found that the 5-year ipsilateral breast tumor recurrence (IBTR) rate was 3.4% in young patients and 1.1% in older patients ($p$<0.001) (Kim et al., 2011). In their study, 24.4% patients were 40 years or younger. Similarly, 27% of our patients were 40 years or younger.

Most studies report that obesity is an independent risk factor for developing distant metastases, but not

locoregional recurrence (Ewertz et al., 2011; Sparano et al., 2012). A few studies have also found associations between low body mass index and locoregional recurrence (Chen et al., 2009). In our study, the risk of recurrence was not related to BMI in a multivariate analysis; the association was observed only in the univariate analysis. Additionally, no association was observed between BMI and the risk of locoregional recurrence. This result may have occurred because of the limited number of patients and short follow-up.

The existence of distinct molecular subtypes of breast cancer has given us the genetic underpinnings to account for the differences in both the natural history and treatment responses of breast cancers. These subtypes are distributed differently between women of different races, which may explain the differences in their presentation and response to treatment (Bowen et al., 2006). This type of clinicopathological correlation is not well established in Chinese women. According to the 2013 St. Gallen surrogate molecular subtype, we observed larger tumor sizes for the luminal B1 subtype than the luminal A subtype. However, luminal B1 tumors had a higher node positivity rate than luminal A tumors. Brouckaert applied the 2011 St. Gallen surrogate molecular subtypes to 4,224 breast cancer patients, and his data showed the same characteristics as our patients with luminal A and luminal B tumors (Brouckaert et al., 2012).

Several studies have examined the associations between breast cancer and molecular subtype. Millar LR et al. used a five-biomarker panel to predict local recurrence for 495 early-stage invasive breast cancers treated with BCS. They found a 5-year locoregional recurrence rate of 15% for HER-2-enriched tumors compared with 1% for luminal A tumors (statistically significant in a univariate analysis) (Millar et al., 2009). K. David Voduc et al. examined 2,985 patients with early-stage breast cancer treated with BCS. With 325 local recurrences and 227 regional lymph node recurrences, a multivariate analysis found that HER-2-enriched and basal subtypes were associated with an increased risk of local and regional recurrence (Voduc et al., 2010). Haffty et al. observed a higher overall incidence of local recurrence in a cohort of 482 patients treated with BCS. The local recurrence rate was 17% at 5 years, and there was no difference between triple-negative patients (TNPs) and non-TNPs (Haffty et al., 2006). Furthermore, Dent et al. (2007) found no difference in local recurrence rates for TN breast cancer in 1,601 patients.

The classification of breast cancers into five subtypes (luminal, HER-2 enriched, normal breast-like, and basal-like) has recently been proposed based on gene expression profiles (Sorlie et al., 2001; Brenton et al., 2005). This classification scheme has been shown to have prognostic significance and implications with respect to response to therapy. However, the established pathological work-up is easier and cheaper and therefore remains the gold standard for estimating the risk for breast cancer relapse and for guiding clinical decisions. Several surrogate panels of prognostic and predictive markers have been proposed and are defined in a variety of ways. The 2011 St. Gallen consensus meeting has recently advised the use of four biomarkers (ER, PR, HER2, and Ki67) as surrogate subtypes, and this panel has been validated against an intrinsic subtype classification (Cuzick et al., 2011). These surrogate subtypes remain approximations of convenience rather than perfectly representing the intrinsic molecular classification.

We used the 2013 St. Gallen recommended surrogate panel definitions and confirmed Brouckaert's conclusion that the luminal A subtype differed significantly from HER-2-enriched and basal-like breast cancers. However, our results did not show a significant difference between the luminal A and luminal B1 subtypes.

Our results are not easily compared with Brouckaert's study for a number of reasons. First, our study included more than 100 patients treated with neoadjuvant therapy, whereas Brouckaert excluded these patients. Second, patients with HER-2 overexpression were routinely treated with trastuzumab beginning in 2005 in his hospital. The HER-2-overexpressing patients in our study never received trastuzumab, and they represented approximately twice the number of patients as that included in Brouckaert's study (20.6% vs. 11.3%, respectively). Third, Brouckaert considered "any nuclear staining" as positive, whereas we used a 1% cutoff for the proportion of positive cells. Fourth, he used tumor grade instead of Ki67, whereas we used the PR level. Finally, all of our patients were treated with BCS.

Despite the short follow-up in our cohort of patients, significant differences in DFS were discernible. Our results indicate a higher risk for local and distant relapse in HER2-enriched breast cancer, but no additional risk in the triple-negative subtype. The relevance of breast cancer subtypes as predictors of local recurrence was not demonstrated.

The limitations of our study should be noted. The retrospective nature of this study carries the risk of introducing bias. In addition, we could not perform subgroup analyses because the number of cases of locoregional relapse in our series was small and the follow-up time was short.

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The author(s) declare that they have no competing interests.

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