Effect of Younger Age on Survival Outcomes in T1N0M0 Breast Cancer: A Propensity Score Matching Analysis

Wenjing Zhong, MD [1#],Luyuan Tan, MD&PhD[1#], Wen G. Jiang, MD&PhD [1,3], Kai Chen, MD [1], Na You, PhD [2], Andrew J. Sanders, PhD [3], Gehao Liang, MD&PhD [1], Zihao Liu, MD&PhD [1], Yun Ling, MD&PhD [1] , Chang Gong, MD&PhD [1]*

[1] Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation and Department of Breast Surgery ,Breast Tumor Center , Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University.

[2] Department of Statistical Science, School of Mathematics and Computational Science & Southern China Research Center of Statistical Science, Sun Yat-sen University, Guangzhou 510275 China

[3] Cardiff China Medical Research Collaborative, Cardiff University School of Medicine, Cardiff University, Heath Park, Cardiff, United Kingdom.

[#] These two authors contributed equally to this work.

***Correspondence:**

Chang Gong

Breast Surgery Department ,Breast Tumor Center

Sun Yat-sen Memorial Hospital, Sun Yat-sen University

107 Yanjiang West Road, Guangzhou 510120, P.R. China

E-mail addresses: changgong282@163.com or gchang@mail.sysu.edu.cn.

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Synopsis: Younger (≤40 yrs) patients with T1N0M0 breast cancer had a poor prognosis independent of other aggressive breast cancer features.

Abstract

Purpose We evaluated the effect of younger age on recurrence risk in Chinese women diagnosed with T1N0M0 breast cancer (BC), using propensity score matching (PSM) analysis.

Methods We included 365 women who were diagnosed with T1N0M0 BC between 2003 and 2016, and who received surgery at our center. They were classified as younger (≤40 yrs) and older (>40 yrs). We used PSM to balance clinicopathologic characteristics between the two age groups. Survival was analyzed by the Kaplan–Meier method, before and after PSM.

Results Over a median follow-up period of 79 months, 54 patients developed recurrences. Before PSM, younger patients had worse RFS than older patients. Significantly worse RFS was seen in younger patients with $HER2^+$ BC compared with their older counterparts. Younger patients had higher rates of loco-regional recurrence rather than metastasis, especially in the first 5 years after diagnosis. After PSM, the two age groups still significantly differed in 5-year RFS.

Conclusion Among PSM pairs with T1N0M0 BC, with equal baselines and treatment conditions, we found that patients who presented at younger ages had worse outcomes, independently of other pathological features. Younger patients with BC may require more individualized therapy to improve their prognosis.

Key words: T1N0M0 breast cancer; Young patients; Recurrence-free survival; Propensity score matching.

Introduction

In recent years, the epidemiology of breast cancer (BC) among Chinese patients has shown intriguing trends. First, age of BC diagnosis is younger among Chinese patients than among western women. Hanrahan et al. reported the median age at diagnosis of early-stage BC to be 65 years among 51,246 patients in the SEER database[1], compared with a median age of 49 years in a study of 868 Chinese women with stage I–III BC[2]. Second, the percentage of patients with BC who are younger than 40 years old in Western countries is only 5–9.6%[3-5], compared with approximately 20% in Asian countries[6-8].

The incidence of invasive but node-negative BC with tumors ≤ 2 cm (T1N0M0) has been increasing. According to a BC screening program(Chinese National Breast Cancer Screening Program ,CNBCSP) among 1.22 million Chinese women, among screening-detected breast cancers in urban and rural women, 62.5% and 66.3% were T1 BC, 46.2% and 38.8% were early stage(0-I) in urban and rural women respectively[9].

Generally, the prognosis of T1N0M0 BC is favorable, with a 5-year recurrence-free survival (RFS) rate about 90%, even without adjuvant chemotherapy (ACT)[1,10,11]. However, BC recurrence is higher in specific subgroups. Several retrospective studies have described prognostic risk factors of T1N0M0 BC, such as human epidermal growth factor receptor 2 (HER2)-positive, triple-negative BC (TNBC), high Ki-67 index, higher tumor grade and younger age[1,11-15]. Considering the increasing incidence of T1N0M0 BC among younger patients in China, survival outcomes among these patients, even with T1N0M0 BC, warrants investigation. Therefore, we applied the propensity score matching (PSM) method to assess the impact of age on survival outcome from T1N0M0 BC in a Chinese cohort.

Materials and Methods

Study population

We retrospectively identified patients with T1N0M0 BC who received surgery between 2003 and 2016 in Sun Yat-sen Memorial Hospital Breast Cancer Center. Eligibility criteria included (1) pathologic diagnosis of T1N0M0 tumor; (2) unilateral BC; and (3) invasive ductal and lobular carcinoma. Patients who (1) received any kind of neoadjuvant therapy; (2) received breast-conserving surgery (BCS) but without radiotherapy; or (3) had multifocal tumors detected by

mammography, ultrasonography and/or magnetic resonance imaging were excluded from this analysis. Finally, 365 T1N0M0 cases were enrolled. All eligible patients received surgical treatment and ACT based on tumor size and pathologic characteristics, according to NCCN guidelines and patients' preference. In our center, adjuvant HER2-targeted therapy was routinely recommended for patients with T1cN0 $HER2^+$ BC, but not for those patients with T1a–bN0 $HER2^+$ BC. Sentinel lymph node biopsy (SLNB) was recommended in principle for all included patients but axillary lymph node dissection (ALND) was performed if the patient refuse to receive SLNB or if SLNB failed. Full ethical approval was granted by Sun Yat-Sen Memorial Hospital Ethics Committee (SYSEC-KY-KS-2018-044).

Data

We collected prospectively registered medical records from the Research Electronic Data Capture system. We divided patients according to their ages at diagnosis into the younger group (≤40 yrs) and the older group (> 40 yrs). For each patient, we retrieved all information on tumor size, lymph node status, histological type, tumor grade, hormonal receptor (HR) status, HER2 status, Ki-67 expression, surgery type and adjuvant therapy. All enrolled patients had been tested for HER2 status according to the testing guideline at the time of diagnosis. Patients who were

diagnosed during 2003–2006 were tested according to the Herceptest® Scoring System[16,17]; those diagnosed during 2007–2012 were tested according to the 2007 ASCO/CAP guideline[18]; and those who diagnosed during 2013–2016 were tested according to the 2013 ASCO/CAP guideline[19].

Estrogen receptors (ER) and progesterone receptors (PR) were considered positive when nuclear expression was observed in at least 1% of the tumor cells. For Ki-67 status, we used ≥14% positive staining as the cut-off for positive and negative results. We classified BC cases into 3 subgroups: HR^+ (ER/PR^+, $HER2^-$) , HER2+ ($HER2^+$, regardless of ER/PR status) and TNBC (ER^-,PR^-, $HER2^-$).

Statistical Methods

Patient characteristics were tabulated and described by median and range. Comparisons between groups were made using the $\chi 2$ test. RFS was defined as interval between the date of diagnosis and the first local or distant disease recurrence or contralateral breast event, or the last follow-up without relevant event, which was further divided into locoregional recurrence-free survival and distant recurrence-free survival. Patients who died before disease recurrence were considered censored at the date of death. Patients who experienced both local and distant recurrences at the

same time were considered to have suffered both events. RFS was estimated by the Kaplan–Meier method. The log-rank test was used to compare survival curves between subgroups according to prognostic factors. All statistical tests were two-sided; $P < 0.05$ was considered significant.

Propensity score matching

Propensity scores (PS) were generated from a logistic regression model described by Rosenbaum and Rubin[20]. Covariates, including tumor size, tumor grade, subtype, Ki-67 expression, breast surgery type and ACT, were selected into the model as reported risk factors to optimize the matching procedure by reducing bias for mortality and recurrence[1,11-15,21,22]. Due to the definition of $HER2^+$ group ($HER2^+$, regardless of HR status), the percentage of patients with HR^+ disease (ER^+ or PR^+, regardless of HER2 status) who needed endocrine therapy was different in the two age groups. However, endocrine therapy did not significantly differ among patients with HR^+ disease between the two age groups before and after PSM (Supplementary Table 2). Therefore, to match more pairs, adjuvant endocrine therapy (AET) was not analyzed in the PSM procedure. In this retrospective study, each patient in the younger group was 1:1 matched, with caliper value of 0, to a corresponding patient in the older group by selecting the same PS for each pair. Both

Kaplan–Meier method and the exact method of McNemar's test were used to compare the survival of the two groups. All statistical analyses were performed by SPSS, version 24.0.

Results

Clinicopathologic characteristics

The median age of the 365 participating women was 50 years, of whom 17% (62/365) were in the younger group (median age: 37 years, range: 26–40 years) and 83% (303/365) were in the older group (median age: 52 years, range: 41–78 years). Their clinicopathological characteristics are shown in Table 1. The younger group tended to have higher Ki-67 expression (P =0.016) and higher tumor nuclear grade (P =0.099). The younger group also showed a trend for higher rates of $HER2^+$ (19.4% vs. 15.8%) and TNBC tumors (14.5% vs. 9.0%), although without statistical significance. Of the 365 participants, 245 (67.1%) underwent BCS with radiotherapy and 120 (32.9%) underwent mastectomies. Because the study only included patients with lymph node-negative disease, no patients who underwent mastectomies received radiation for negative axillary lymph node. Younger patients tended to have lower compliance to the AET than older patients (74.2% vs. 83.2%, P=0.096). Among patients with HR^+ tumors (312/365), 90.2% (46/51) of the younger patients and 96.5% (252/261) of the older patients received AET

(Supplementary Table 2), and 314 patients (86.0%) received ACT. Among the 60 patients with $HER2^+$ tumors (T1a–bN0: *n*=20, T1cN0: *n*=40), 53.3% (32/60) of $HER2^+$ patients with T1cN0 tumors received standard one-year adjuvant trastuzumab therapy; 13.4% (8/60) of patients with T1cN0 tumors only received adjuvant trastuzumab therapy for half a year, due to financial issues; and 33.3% (20/60) patients were not recommended to undergo adjuvant HER2 targeted therapy for T1a–bN0 tumors. Younger patients were more likely to have BCS with radiotherapy than older patients (77.4% vs 59.1%, *P* =0.058).

Recurrence and prognosis before PSM

For the cohort as a whole, median follow-up was 79 months (range: 13–125 months); both 5-year OS (96.6%) and 10-year OS (94.0%) were very favorable. However, 54 patients experienced recurrences, including 24 locoregional recurrences, 28 distant metastases, 6 contralateral breast events and 4 patients with both locoregional and distant recurrences. Kaplan–Meier survival curves showed younger patients had a significant lower 5-year RFS rate (younger: 80.6%, older: 89.1%, *P* =0.049; Figure 1). When stratified by site and time of recurrence(Table 2), younger age was associated with significantly higher rates of all recurrences and locoregional recurrences (14.5% vs 5.0%, *P* =0.004), but not with distant recurrences (younger: 6.5%, older: 7.9%, *P*

=0.795) or contralateral breast events (younger: 6.5%, older: 0.7%, *P* =0.229). Younger patients had a significantly higher rate of recurrence for Years 0–5 than older patients, but not for Years 5–10.

Survival analysis based on subtypes and age showed that younger patients with the $HER2^+$ subtypes had worse RFS than older patients (*P* =0.006), but did not significantly differ in RFS for those with HR^+ BC (*P* = 0.845) or TNBC (*P* =0.390). The subgroup with the worst 5-year RFS estimate were younger patients with $HER2^+$ tumors (50.0%; Table 3).

Recurrence and prognosis after PSM

After PSM, we had 60 pairs (60 younger patients and 60 older patients) from 62 younger patients and 303 older patients; the two members of each pair were consistent in the above 6 matching covariates except age (Table 1). Among the 60 younger patients after PSM, 12 had recurrence events within 5 years. The other 48 patients showed no recurrences over ≥5 years of follow-up visits. Follow-up periods and outcomes of patients before and after PSM are shown in Supplementary Table 1. For patients whose BC recurred within 5 years, although they were not followed up for 5 years, as long as their paired patients survived over 5 years, these pairs were comparable. However, 5-year RFS still significantly differed between the age groups (younger:

80.0%, older: 96.7%, *P* =0.015; Figure 2) after PSM. Then, as the samples were matched into pairs, the paired chi-square test (McNemar's test) was used to unravel the impact of age on 5-year survival in a paired sample unit. In Table 4, for 46 pairs, outcomes of the two age members were similar (survived for ≥5 years without recurrence); in no pairs did both members relapsed within 5 years. However, for 14 pairs (12+2), outcomes of the two age members were different. The McNemar's test was applied to the 14 outcome-discordant pairs to figure out if younger members of the pairs were significantly more likely to relapse within 5 year than the older members. We found that the younger members of the pairs were significantly more likely to relapse within 5 years than the older members (*P*=0.013), which shows the effect of age on prognosis.

Discussion

The major finding of this retrospective study is that after using PSM to adjust for a series of clinicopathologic features and treatment strategy, age ≤40 years at presentation is an independent prognostic risk factor, associated with worse 5-year RFS rates in patients with T1N0M0 BC, and particularly so for younger patients with $HER2^+$ T1N0M0 BC.

In previous studies of prognostic risk factors (including age) for T1N0M0 BC, patients who received ACT were often excluded from analyses[12,23]. However, as NCCN guidelines recommend ACT with or without target therapy for T1b–c patients, excluding patients treated with ACT cannot reflect the real-world impact of age on prognosis. In our study cohort, 86% patients received ACT. By including ACT as a PSM variate, the impact of age on survival was more accurately estimated. Our results indicate that younger BC patients have a worse prognosis, independent of other factors associated with aggressiveness, including HER2 status, even among patients with T1N0M0 disease. However, NCCN guidelines for T1N0M0 BC treatment are only based on tumor size and subtype; younger patient age is not among the recommended criteria for choosing a treatment strategy. Breast cancer in younger women is an aggressive disease, even for those with T1N0M0 BC, thus, individualized treatment should be considered, especially in Asian populations, which have a higher percentage of younger patients with T1N0M0 BC. Anders et al suggests that younger women can be characterized by lower hormone sensitivity and higher HER2 expression by using genomic expression analysis[24] which might explain the poor prognosis. Also, Johnson et al found expression differences in age-related genes (*KRT5*, *KRT6A*, *KRT6B* and *EGFR*) within and across BC subtypes, which were significantly associated with

inferior prognosis in younger women[25]. Together, these findings highlight the need to re-examine treatment strategies for younger patients with T1N0M0 BC.

In subtype analysis, we observed a significantly worse 5-year RFS for younger women diagnosed with $HER2^+$ BC compared with their older counterparts (50.0% vs. 85.4%, P =0.006). However, because of the small numbers of patients, this point estimate has a wide confidence interval. A previous study suggested that trastuzumab-based ACT may reduce both early recurrence and mortality in $HER2^+$ tumors that are $\leq$ 1 cm[12], although many clinicians might not recommend ACT in view of the small benefit balanced against costs and toxicity[10]. A study of outcomes of 1102 patients with T1a–bN0M0 BC showed that patients <35 years old with $HER2^+$ tumors had the worse 5-year RFS[23]. This result is consistent with our research, which suggests that age should be considered when deciding on adjuvant therapy for $HER2^+$ T1N0M0 BC; these patients may be more likely to benefit from trastuzumab-based ACT. According to the NCCN guidelines, cyclophosphamide (C) plus trastuzumab (T) is recommended for T1c $HER2^+$ rather than T1a–b tumors. Our results indicate that patients younger than 40 years old with HER2+ had a higher rate of recurrence. Therefore, prospective clinical trials are needed to find a regimen that delivers the optimal survival benefit with fewer adverse reactions for this population. However, the effect

of age on HR^+ tumors was not significant. Some studies suggested that although younger women had high rates of AET, nonadherence may have led to inadequate treatment efficacy in younger women and contribute to poor outcomes for HR^+ patients[26,27]. In our cohort, 96% HR^+ women received AET, and even younger patients achieved more than 90% compliance to the treatment. Good adherence to treatment may reduce the poor effects of age on prognosis. Among patients with TNBC, we observed no difference between the two age groups. Ford et al. observed that 5.3 % of BCs in patients ≤40 years old were attributable to *BRCA1* mutations, compared with 2.2% in 40–49 year-olds and 1.1 % in 50–70 year-olds[28]. Patients with *BRCA1* mutations were more likely to develop basal-like BCs, including the triple-negative subtype[29,30]. The underlying biology may help explain the relationship between age and TNBC.

We also found that, before PSM, younger patients had significantly higher rates of the locoregional recurrence rather than metastasis in the first five year after diagnosis. In recent years, comprehensive therapy have helped improve local control after breast-conserving surgery, although the local recurrence rate for younger patients who undergo BCS was significantly higher than that of those undergo mastectomy[22]. In our cohort, 245/365 (67.1%) of women received BCS and the percentage of younger patients received BCS was higher than older patients (48/62

[77.4%] vs. 197/303 [59.1%]). A meta-analysis of 19 studies included showed that after BCS, younger BC patients are at higher risk of local recurrence within 5 years (RR: 2.64, 95% CI: 1.94–3.60) and 10 years RR: 2.37, 95% CI: 1.57–3.58) than older patients[31]. Several factors may contribute to locoregional recurrence for younger women. First, whereas preoperative imaging of multifocal tumors can help identify choose optimal surgical approaches, a higher percentage of younger patients have higher mammographic density than do older patients[32], which may decrease mammographic sensitivity (masking bias); this effect seems to be more obvious in small tumors[33]. However, digital mammography, ultrasonography, and magnetic resonance imaging may increase cancer detection in women with high mammographic density. Although multifocal tumors were excluded from our study, the relationship between preoperative imaging assessment and recurrence rate after BCS in younger patients with T1N0M0 BC warrants further study. Furthermore, studies that use gene expression micro-array technology have demonstrated patterns that correlate with local recurrence in younger women[34]. However, data on related genes were not available in our material. In addition, the relatively short follow-up period may not be sufficient to observe differences in long-term locoregional recurrence and metastasis between the two age groups.

Our study had several limitations. First, it was a retrospective single-institution study, which lent inherent bias. Second, during the study period of 13 years, continuous optimization of treatment regimens may have varying effects on prognosis of the two age groups. Third, other important information, such as Oncotype DX and MammaPrint were not available. However, after adjusting for known prognostic factors using PSM, our results suggested that recurrence in women younger than 40 years old with T1N0M0 BC were significantly higher than for older patients. Few studies of preoperative imaging evaluation, surgery selection and postoperative therapy for younger patients with T1N0M0 BC are available. Studies based on genetic information and a larger sample size are therefore needed to evaluate the effect of age on prognosis.

Conclusions

Among patients with T1N0M0 BC, age of 40 years or younger is a prognostic risk factor independent from other aggressive features, including HER2 status. We found the recurrence rate for younger patients with T1N0M0 BC to be significantly higher than for older patients, especially for those with the $HER2^{+}$ subtype. Therefore, treatment decisions for T1N0M0 BC should consider age as a prognostic factor together with subtype and other tumor characteristics.

Younger T1N0M0 patients might benefit more from more comprehensive evaluation and individualized treatment.

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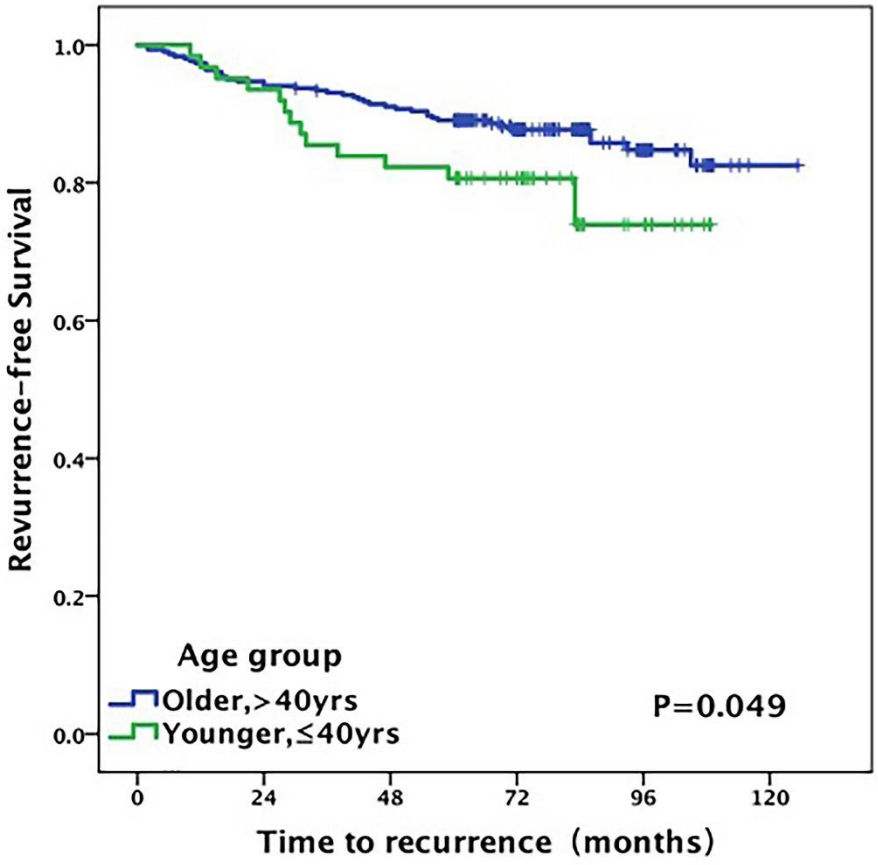
Figure legends

Figure 1 Recurrence-free survival by age at diagnosis before PSM;

Figure 2 Recurrence-free survival by age at diagnosis after PSM.

Abbreviations and acronyms used in the figure

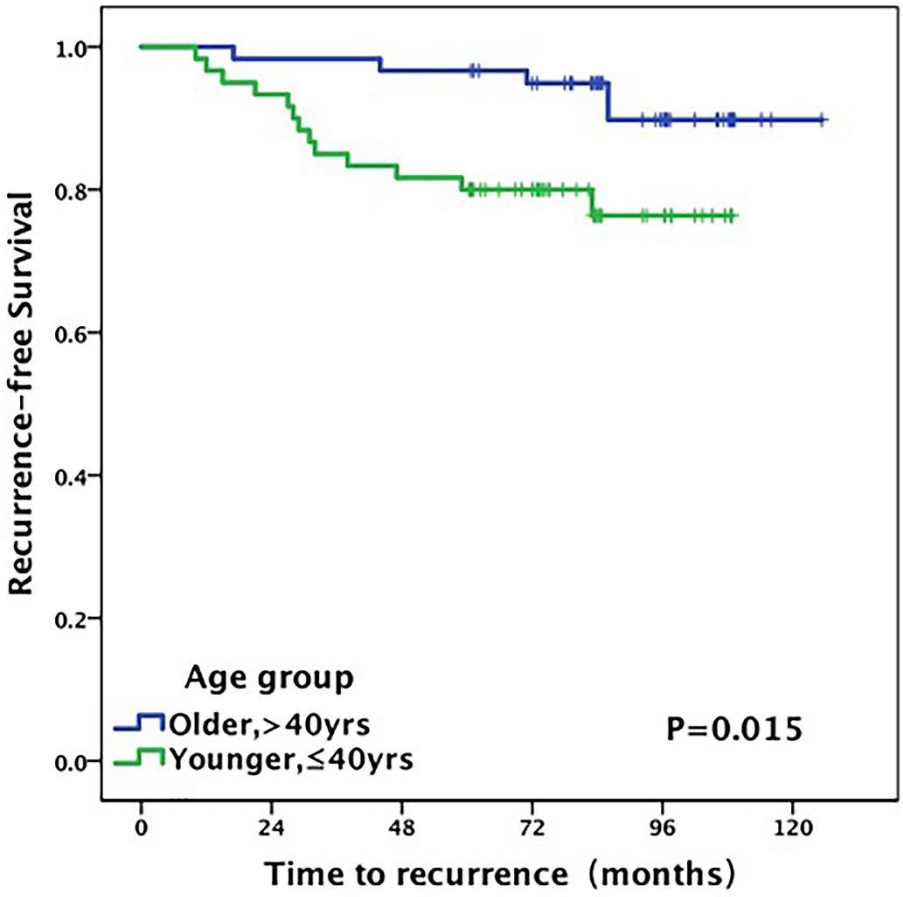
PSM propensity score matching



Number at risk

Older	302	286	274	185	71	1
Younger	62	58	51	34	13	0
Time (m)	0	24	48	72	96	120

Figure 1



Number at risk

Older	60	59	58	53	32	1
Younger	60	56	49	32	11	0
Time (m)	0	24	48	72	96	120

Figure 2

Table 1. Patient characteristics by age of diagnosis, before and after [a]PSM

Characteristics	**≤40yrs**		**>40yrs**		***P***	**Characteristics**	**≤40yrs**		**>40yrs**		***P***
before PSM	**n=62**	**17.0(%)**	**n=303**	**83.0(%)**		**after PSM**	**n=60**	**50(%)**	**n=60**	**50(%)**	
Subtype						**Subtype**					
[b]HR+ (n=269,73.7%)	41	66.1	228	75.2		[b]HR+ (n=82,68.3%)	41	68.3	41	68.3	
[c]Her-2+ (n=60,16.4%)	12	19.4	48	15,8		[c]Her-2+ (n=24,20.0%)	12	20.0	12	20.0	
[d]TNBC (n=36,9.9%)	9	14.5	27	9.0	0.272	[d]TNBC (n=14,11.7%)	7	11.7	7	11.7	1.000
Histology						**Histology**					
Ductal (n=320,87.7%)	56	90.3	264	87.1		Ductal (n=108,90.0%)	55	91.7	53	88.3	
Lobular (n=45,12.3%)	6	9.7	39	12.9	0.486	Lobular (n=12,10.0%)	5	8.3	7	11.7	0.543
T-stage						**T-stage**					
T1a-1b (n=103,28.2%)	21	33.8	82	27.1		T1a-1b (n=38,31.7%)	19	31.7	19	31.7	

T1c (n=262,71.8%)	41	66.2	221	72.9	0.278	T1c (n=82,68.3%)	41	68.3	41	68.3	1.000
Grade						**Grade**					
I-II (n=288,62.4%)	33	53.2	195	64.4		I-II (n=66,55.0%)	33	55.0	33	55.0	
III (n=137,37.6%)	29	46.8	108	35.6	0.099	III (n=54,45.0%)	27	45.0	27	45.0	1.000
Ki-67						**Ki-67**					
<14% (n=105,28.8%)	10	16.1	95	31.4		<14% (n=20,16.7%)	10	16.7	10	16.7	
≥14% (n=260,71.2%)	52	83.9	208	68.6	0.016	≥14% (n=100,83.3%)	50	83.3	50	83.3	1.000
Surgery Type						**Surgery Type**					
[e]BCS+[f]RT (n=245,67.1%)	48	77.4	197	59.1		[e]BCS+[f]RT (n=84,70.0%)	47	78.3	47	78.3	
Mastectomy (n=120,32.9%)	14	22.6	106	40.9	0.058	Mastectomy (n=36,30.0%)	13	21.7	13	21.7	1.000
[g]SLNB only (n=293,80.3%)	54	87.1	239	78.9		[g]SLNB only (n=97,80.8%)	52	86.7	45	75.0	
[h]ALND (n=72,19.7%)	8	12.9	64	21.1	0.138	[h]ALND (n=23,19.2%)	8	13.3	15	25.0	0.104

Adjuvant Endocrine therapy						**Adjuvant Endocrine therapy**					
Yes(n=298,81.6%)	46	74.2	252	83.2		Yes(n=90,75.0%)	46	76.7	44	73.3	
No(n=67,18.4%)	16	25.8	51	16.8	0.096	No(n=30,25.0%)	14	23.3	16	26.7	0.673
Adjuvant chemotherapy						**Adjuvant chemotherapy**					
Yes(n=314,86.0%)	57	92.0	257	84.8		Yes (n=110,91.7%)	55	91.7	55	91.7	
No(n=51,14%)	5	8.0	46	15.2	0.141	No (n=10,8.3%)	5	8.3	5	8.3	1.000

Abbreviations:

a. PSM: propensity score matching

b. HR+: ER^+ or PR^+, $HER2^-$

c. Her-2 +: ER+ or ER−, PR+ or PR−

d. TNBC:ER^-,PR^-, $HER2^-$

e. BCS: breast-conserving surgery

f. RT: radiotherapy

g. SLND: sentinel lymph node biopsy

h. ALND: axillary lymph node dissection

Table 2. Recurrence for both age groups by site and time of recurrence

	All patients	**Age groups**		**Log-rank**
	n=365	≤40yrs(n=62)	>40yrs(n=303)	***P-value***
All recurrence, n (%)	54 (14.8)	14 (22.6)	40 (13.2)	0.049
[a]Site of recurrence, n (%)				
Locoregional recurrence	24 (6.6)	9 (14.5)	15 (5.0)	0.004
Distant recurrence	28 (7.7)	4 (6.5)	24 (7.9)	0.795
Contralateral breast event	6 (1.6)	4 (6.5)	2 (0.7)	0.229
Time of Recurrence, n (%)				
0-5 years	45 (12.3)	12 (19.4)	33 (10.9)	0.034
5-10 years	9 (2.5)	2 (3.2)	7 (2.3)	0.493

a. Four patients had both locoregional and distant recurrence at same time

Table 3. Recurrence-free survival by age groups and breast cancer subtype

Subtype	Age groups	Patients at risk (n)	Recurrence (n)	5-Year [d]eRFS(95% CI)	*P-value*
[a]HR+	≤40yrs	41	4	90.2 (0.812, 0.992)	
	>40yrs	228	26	91.2 (0.875, 0.949)	0.845
[b]Her-2+	≤40yrs	12	6	50.0 (0.218, 0.782)	
	>40yrs	48	7	85.4 (0.754, 0.954)	0.006
[c]TNBC	≤40yrs	9	4	70.8 (0.436, 0.980)	
	>40yrs	27	7	77.3 (0.612, 0.934)	0.390

Abbreviations:

a. HR+: ER^+ or PR^+, $HER2^-$

b. HER2+: $HER2^+$, ER^+ or ER^-, PR^+ or PR^-

c. TNBC: ER^-, PR^-, $HER2^-$

d. eRFS: estimated recurrence-free survival

Table 4. A 2*2 Contingency table, using matched pairs (*n*=60) as the sampling units

	Outcome of patients >40yrs (pairs)			
Outcome of patients ≤40yrs (pairs)	Did not recur for 5yrs	Recurred within 5yrs	**Total(n)**	***P-value***
Did not recur for 5yrs	46	2	48	
Recurred within 5yrs	12	0	12	
Total(n)	58	2	60	0.013

Supplementary Table 1 Outcome and follow-up time by age of diagnosis before and after [a]PSM

Characteristics	≤40yrs (n=62,17.0%)		>40yrs (n=303,83.0%)		Characteristics	≤40yrs (n=60,50%)		>40yrs n=(60,50%)	
Before PSM	Recurred within 5yrs (n=13)	Did not recur for 5yrs (n=49)	Recurred within 5yrs (n=33)	Did not recur for 5yrs (n=270)	**After PSM**	Recurred within 5yrs (n=12)	Did not recur for 5yrs (n=48)	Recurred within 5yrs (n=2)	Did not recur for 5yrs (n=58)
Follow-up([b]RFS)					**Follow-up(RFS)**				
<5yrs	**13**	**0**	**33**	**2**	**<5yrs**	**12**	**0**	**2**	**0**
≥5yrs	**0**	**49**	**0**	**268**	**≥5yrs**	**0**	**48**	**0**	**58**

Abbreviations:

a. PSM: propensity score matching

b. RFS: Recurrence-free survival (The interval between the date of diagnosis and the first local or distant disease recurrence, or contralateral breast recurrences event, or the last follow-up without relevant event).

Supplementary Table 2 Adjuvant endocrine therapy among HR-positive patient by age of diagnosis before and after [a]PSM

[b]HR-positive	≤40yrs(n=62)		>40yrs(n=303)		*[c]P*	HR-positive	≤40yrs(n=60)		>40yrs(n=60)		*[c]P*
before PSM	**n=51**	**82.2(%)**	**n=261**	**86.1(%)**		**after PSM**	**n=51**	**85.0(%)**	**n=48**	**80.0(%)**	
Adjuvant endocrine therapy						**Adjuvant endocrine therapy**					
Yes(n=298,95.5%)	46	90.2	252	96.5		Yes(n=90,90.9%)	46	90.2	44	91.7	
No(n=14,4.5%)	5	9.8	9	3.5	0.102	No(n=9,9.1%)	5	9.8	4	8.3	1.000

Abbreviations:

a. PSM: propensity score matching

b. HR positive group: ER^+ or PR^+, $HER2^-$ or $HER2^+$)

c. P for Continuity Correction