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Original Article

Treatment and long-term outcome of breast cancer in very young women: nationwide population-based study

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Abstract

Background: The study aimed to assess the correlation between long-term survival and treatment in very young women with breast cancer.

Methods: Data on women with breast cancer were retrieved from the Taiwan Cancer Registry between 2004 and 2014. Patients who did not undergo surgery or who had stage 0 or IV disease were excluded. Survival analysis was conducted. The participants were divided into very young (20–29.9 years), young (30–39.9 years), and adult (40–50.0 years) groups.

Results: Among 104 115 women, 24 474 (572 very young, 5565 young, and 18 337 adult) were eligible for the study. Median follow-up was 79.5 (range 24–158) months. The mortality rates in the very young, young, and adult groups were 12.9, 10.0, and 8.2 per cent respectively ($P < 0.001$). Very young patients had higher histological grade, unfavourable subtype, higher TNM stage, and received more breast-conserving surgery (BCS). Kaplan–Meier survival analysis showed that very young patients had the poorest long-term survival. Very young patients with stage II disease had the worst prognosis. In the multivariable regression model, radiotherapy was associated with decreased local recurrence but not with improved overall, cancer-specific, or disease-free survival for stage II disease in the very young group. Surgery type and chemotherapy were not associated with significant improvement in overall survival.

Conclusion: Very young patients with stage II disease had poor long-term outcomes. BCS had no detrimental effects on long-term outcomes.

Introduction

Breast cancer is the most common cancer in women worldwide and in Taiwan[1,2]. Its incidence has increased in recent decades probably owing to environmental factors, dietary habits, and advancements in diagnostic modalities[3]. In Taiwan, breast cancer usually occurs in individuals aged between 45 and 55 years[4], about 10 years younger than in western countries, which may lead to significant excess costs in medical treatment and productivity loss. The absolute number of young women at risk of developing breast cancer is growing, making it a significant health issue for this population[5]. Breast tumours in younger women are more aggressive and advanced, are more likely to be caused by an inherited defective gene (such as breast cancer susceptibility gene (*BRCA*) mutation), and may respond differently to treatment than tumours in older women[6,7]. This population is usually faced with a variety of issues and psychosocial considerations, including fertility preservation, body image, and the impact of disease on family life, relationships, genetic counselling, career, and finances[6,8,9].

Multimodal therapy has been recommended in the treatment of patients with breast cancer, including younger patients. Whether these treatment types offer optimal outcomes in younger patients as in older patients remains under debate. Conventionally, surgical treatments for breast cancer include breast-conserving surgery (BCS) and mastectomy[10,11]. The former option, with its restricted cosmetic alteration and improved quality of life, might prompt young patients to undergo limited therapy. A meta-analysis[12] of registry and database studies conducted in 22 598 patients aged below 40 years suggested that BCS had disease-free and overall survival equivalent to those of mastectomy; however, a meta-analysis[13] of studies including 3531 young patients with locally advanced breast cancer after neoadjuvant therapy showed that BCS was associated with better disease-free and overall survival. Additionally, younger age (less than 35 years) has been considered a relative contraindication to BCS[14]. Local recurrence after BCS is a primary concern, so adjuvant radiotherapy should be administered to patients having this treatment.

Breast cancer is relatively rare in very young patients (aged less than 30 years). Although younger patients have been generally defined as those younger than 40 years, previous literature

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defined younger patients with breast cancer as those aged less than 50 years[7,15], 45 years[5], or 40 years[8,16–18]. Studies of very young patients remain scarce, probably due to the limited number of patients. Hence, there are limited data regarding the characteristics, treatment patterns, and outcomes of very young patients with breast cancer. The aim of this study was to investigate the treatments and long-term survival of very young patients with breast cancer, and the differences in outcomes between very young patients and other young patients with breast cancer.

Methods

Study population

The target population was women aged 20.0–29.9 years with breast cancer registered in the Taiwan Cancer Registry (TCR). Candidates were patients with a C50 (breast cancer) code according to the ICD-O-3, diagnosed from January 2004 to December 2014. For comparison, women aged 30–50 years with breast cancer were also included. Patients who had stage 0 or IV disease, those whose pathological report did not indicate ductal carcinoma (DC) or lobular carcinoma (LC), and those who did not undergo surgery were excluded. The TCR (from the Health Promotion Administration), which includes 85 per cent of patients with newly diagnosed breast cancer, contains prospectively collected data on patients, tumour characteristics, types of treatment, and follow-up[19]. Data in the TCR were linked to the National Health Insurance Research Database (NHIRD, 2003–2014) and the Death Registry (2003–2014) to allow retrieval of independent variables and dependent variables. Enrolled patients were divided into three groups: very young (20.0–29.9 years), young (30.0–39.9 years), and adult (40.0–50.0 years).

Independent variables

Potential prognostic variables included patient characteristics (age and sex), co-morbidity (Charlson Co-morbidity Index, diabetes mellitus, and hypertension), disease characteristics (laterality, tumour location, tumour size, histological grade of cell differentiation, molecular intrinsic subtype, pT, and pN), initial treatment type (BCS or mastectomy), and therapeutic characteristics (hormone therapy, chemotherapy, and radiotherapy). The specification of co-morbidity (Deyo version) by ICD-9 clinical modification code included 17 diseases[20]. The molecular intrinsic subtypes included oestrogen receptor (ER)/progesterone receptor (PR)-positive (luminal A and luminal B), human epidermal growth factor receptor 2 (HER2)/*neu* proto-oncogene-overexpressing, and basal-like[21]. Luminal A and B (including B1 and B2) were defined as ER/PR-positive. Additionally, luminal B1 and B2 were defined as ER/PR-positive with high cell grade or ER/PR-positive with HER2/*neu*-positive status respectively. HER2/*neu* overexpression was defined as HER2/*neu*-positive but ER/PR-negative breast cancer. Triple-negative breast cancer (TNBC) was an ER/PR-negative and HER2/*neu*-negative subtype. Hormone therapy included tamoxifen, letrozole, exemestane, and anastrozole. Chemotherapy included anthracyclines (doxorubicin and Lipo-Dox®) and taxanes (paclitaxel and docetaxel), whereas immunotherapy included trastuzumab[22,23]. Data on co-morbidity (Charlson Co-morbidity Index, Deyo version), chemotherapy, and hormone therapy were retrieved from the NHIRD. Because the National Health Insurance system in Taiwan is a one-payer system (regulated by the National Health Insurance Administration), this database covers healthcare billing services of all patients. Therefore, accurate data on co-morbidity and medication could be retrieved.

Dependent variables

The primary endpoint was overall survival, which referred to the percentage of patients who were alive for a certain period of time after diagnosis of breast cancer. Secondary endpoints included cancer-specific and disease-free survival, and local recurrence-free rate. Cancer-specific survival referred to the percentage of patients who had not died from breast cancer-related causes for a certain period of time after diagnosis of breast cancer. Disease-free (progression-free) survival and local recurrence-free survival were defined as the percentage of patients who remained disease-free (no distant metastasis or local recurrence) or local recurrence-free for a certain period of time after diagnosis of breast cancer respectively. The Death Registry provides the date and cause of death, and survival outcomes (overall survival and cancer-specific survival) could be validated by linking the TCR to the 2011–2014 Death Registry (from the Ministry of Health and Welfare). The institutional review board at Taipei City Hospital approved this study and waived the requirement to obtain informed consent (TCHIRB-10802009-W).

Statistical analysis

Demographic, clinical, pathological, and therapeutic variables are reported as numbers with percentages. The χ^2 test was used to compare categorical variables between very young patients (aged 20.0–29.9 years), young patients (aged 30.0–39.9 years), and adult patients (40.0–49.9 years). Kaplan–Meier plots were prepared to calculate survival estimates, and significance determined by means of the log rank test. Univariable and multivariable Cox proportional hazards models (using all potential but not highly correlated prognostic factors) were used to assess the crude and independent prognostic values of age and treatment modalities (including surgery, chemotherapy, and radiotherapy) on survival outcomes (overall, cancer-specific, and disease-free survival, and local recurrence-free rate). Hazard ratios (HRs) with 95 per cent confidence intervals are reported. SAS® version 9.2 (SAS Institute, Cary, NC, USA) was used for the initial database-merging process, and SPSS® version 21 (IBM, Armonk, NY, USA) for data management and inferential statistical analysis. All *P* values were two-sided, and the significance level was set at $P < 0.05$.

Results

Initially, 104115 women who were newly diagnosed with breast cancer between January 2004 and December 2014 were identified. Of these, 68 139 had breast DC or LC which was not stage 0 or IV. After excluding 7568 patients who did not undergo surgery and 36 097 who were not aged 20–50 years, a total of 24 474 women with breast cancer (DC: 23 574, 96.3 per cent; LC: 900,3.7 per cent) were enrolled in this study (*Fig. 1*).

Demographic, clinical, and interventional characteristics of patients in the very young (572, 2.3 per cent), young (5565, 22.7 per cent), and adult (18 337, 74.9 per cent) groups are summarized in *Table S1*. The mean(s.d.) age of the cohort at diagnosis was 43.0(5.3) years. Tumour laterality and location did not differ between the groups. Although the very young group had a higher incidence of carcinoma *in situ* (4.4 per cent) and a lower Charlson Co-morbidity Index score than the other two groups, these patients had tumours with a poorer histological grade (42.8 per cent *versus* cohort average 32.1 per cent) and a higher rate of tumours of 2–5 cm in size (52.1 per cent *versus* average 47.3 per

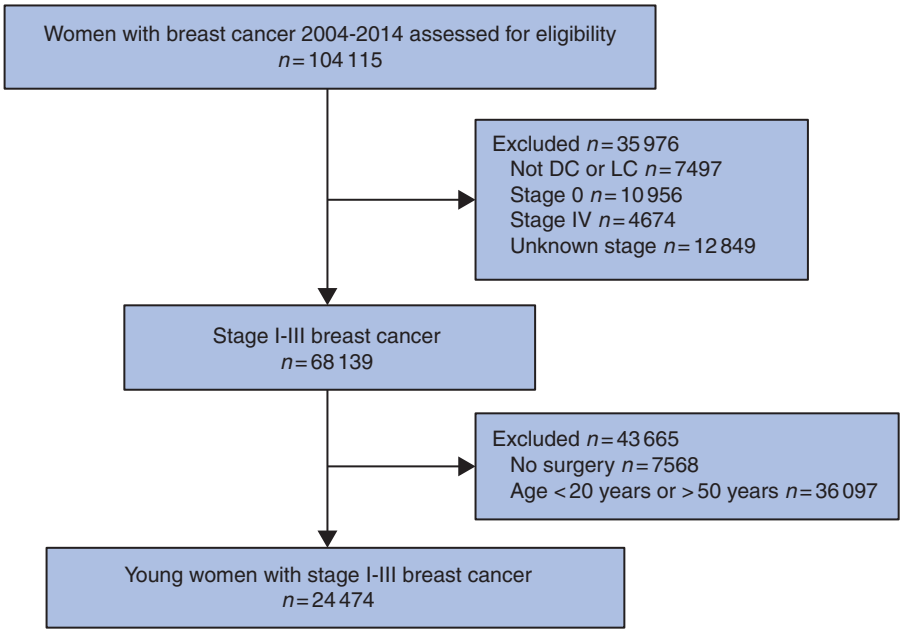

Fig. 1 Study flow chart

DC, ductal carcinoma; LC, lobular carcinoma.

cent). The percentage of patients in the very young group who underwent BCS as the first treatment (62.4 per cent) was higher than that of patients in the young group (50.5 per cent) and the adult group (45.1 per cent) ($P < 0.001$).

The very young group had a higher rate of HER2/*neu* overexpression (8.0 per cent *versus* average 6.4 per cent) and a higher incidence of the triple-negative subtype (18.1 per cent *versus* average 8.6 per cent). Similarly, the incidence of hormone-positive tumours was lower in the very young group (69.6 per cent *versus* average 82.0 per cent; $P < 0.001$). The very young group also had a higher proportion of late-stage tumours (stage II: 57.0 per cent *versus* average 50.9 per cent; stage III: 9.8 per cent *versus* average 8.6 per cent).

Neoadjuvant therapy was more frequently performed in younger patients than in older patients (very young 16.1 per cent, young 13.5 per cent, adult 9.5 per cent; $P < 0.001$), but this trend was not observed for overall chemotherapy (72.2, 75.9, and 73.4 per cent respectively; $P < 0.001$). Anthracyclines and/or taxanes were administered to 66.5 per cent of patients (anthracyclines 63.4 per cent; taxanes 33.0 per cent) as chemotherapy agents. The most frequently administered anthracycline and taxane for very young women were doxorubicin (47.7 per cent, 273 of 572) and docetaxel (32.2 per cent, 184 of 572) respectively. The very young (7.9 per cent, 45 of 572) and young (7.9 per cent, 441 of 5565) groups had higher percentages of trastuzumab administration than the adult group (7.0 per cent, 1275 of 18 337). The very young group had a lower percentage of hormone therapy (69.6 per cent, 398 of 572), but a higher proportion of these patients underwent radiotherapy (61.0 per cent, 349 of 572) than in the young and adult groups ($P < 0.001$).

Median follow-up was 79.5 (range 24–158) months. Overall and cancer-related mortality rates for the cohort at the end of the study were 8.7 per cent (very young 12.9 per cent, young 10.0 per cent, adult 8.2 per cent; $P < 0.001$) and 7.5 per cent (very young 12.1 per cent, young 9.0 per cent, adult 6.8 per cent; $P < 0.001$) respectively. The overall cohort had a disease-free survival rate of 88.8 per cent (very young 84.3 per cent, young 86.7 per cent, adult 89.6 per cent; $P < 0.001$). *Fig. 2* shows Kaplan–Meier survival plots according to age group ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.098$ for overall, cancer-specific, and disease-free survival, and local recurrence-free status respectively).

The P values for pairwise comparisons between any two groups (*Fig. 2a–c*) were less than 0.001, except those for overall survival (very young *versus* young; $P = 0.036$), cancer-specific survival (very young *versus* young; $P = 0.021$), and disease-free survival (very young *versus* young; $P = 0.129$). P values for local recurrence among very young *versus* young ($P = 0.680$) and young *versus* adult ($P = 0.479$) groups were not significant (*Fig. 2d*).

Among the 24 474 patients with stage I–III breast cancer, 3-, 5-, and 10-year overall survival rates in the very young group were 95.2, 90.2, and 81.8 per cent respectively. The 3-, 5-, and 10-year cancer-specific survival rates in this group were 95.3, 90.5, and 82.6 per cent respectively. Respective 3-, 5-, and 10-year disease-free survival rates in the very young group were 93.7, 89.0, and 79.1 per cent. The very young group had the worst overall, cancer-specific, and disease-free survival rates, followed by the young group.

Univariable Cox regression analysis of all cohorts showed that age at diagnosis was a prognostic factor (*Table S2*). The adult (HR 0.76, 95 per cent c.i. 0.66 to 0.87, $P < 0.001$) and young (HR 0.79, 0.69 to 0.91, $P = 0.001$) groups had better overall survival than the very young group. Other prognostic factors included tumour behaviour, tumour size, histological grade, surgery type, resection margin, TNM stage, co-morbidity, radiotherapy, chemotherapy, and hormone therapy. Except for local recurrence-free rate, survival outcomes in the very young group differed from those of the young and adult groups among patients with stage II disease (*Table 1*).

In the multivariable Cox regression model, the adult (HR 0.68, 0.54 to 0.86; $P = 0.002$) and young (HR 0.80, 0.62 to 1.02; $P = 0.067$) groups were associated with better overall survival than the very young group. Similarly, cancer-specific survival was better in the adult (HR 0.62, 0.48 to 0.79; $P < 0.001$) and young (HR 0.77, 0.60 to 0.99; $P = 0.043$) groups. No significant intergroup differences were

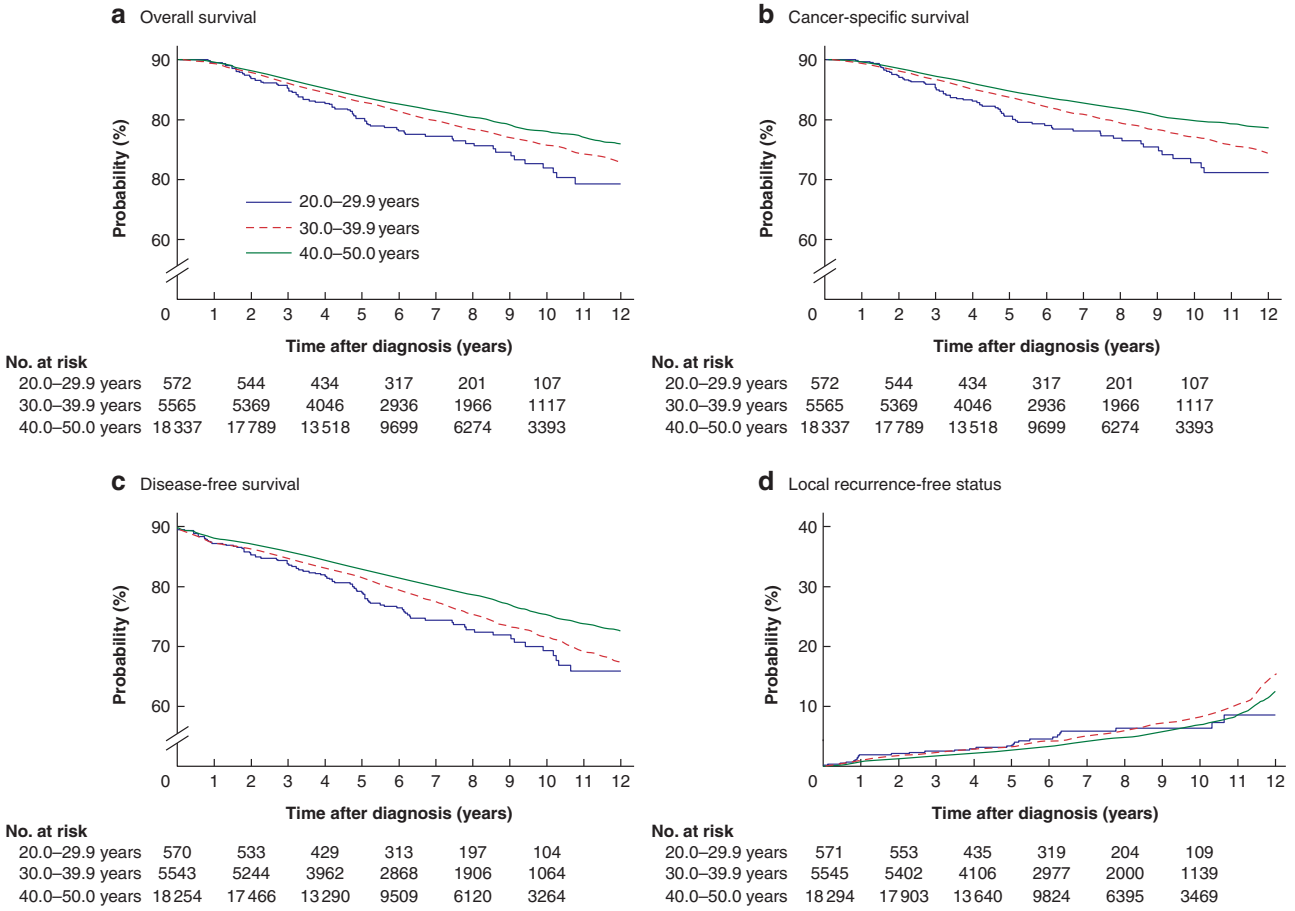

Fig. 2 Kaplan-Meier curves for outcomes of breast cancer according to age

a Overall survival, **b** cancer-specific survival, **c** disease-free survival, and **d** local recurrence-free status. **a** $P < 0.001$, **b** $P < 0.001$, **c** $P < 0.001$, **d** $P = 0.098$ (log rank test).

observed in the HRs for disease-free survival and local recurrence-free rate, except for disease-free survival in the adult group *versus* very young group (HR 0.72, 0.58 to 0.89; $P = 0.003$) (*Table 2*).

Additional stage-specific analyses of the multivariable Cox regression model showed that surgery type (mastectomy *versus* BCS) was not significantly associated with overall, cancer-specific, or disease-free survival, or local recurrence in very young patients with stage I, II, or III disease (*Table 3*). Although chemotherapy might decrease the local recurrence rate among patients with stage I, II, and III disease in the adult and young groups, it was not associated with significantly better overall survival or less local recurrence in very young patients with stage I and II disease. Radiotherapy was associated with improved overall and cancer-specific survival in the adult (stage II and III) and young (stage I and III) groups, but not in the very young group. It was associated with decreased local recurrence (HR 0.14, 0.03 to 0.72; $P = 0.018$) of stage II disease in the very young group. Hormone therapy was associated with improved overall, cancer-specific, and disease-free survival, and the local recurrence-free rate in the adult (stages II and III) and young (stage III) groups, but not in the very young group.

Discussion

This study evaluated four long-term outcomes and the effect of treatment in very young patients with breast cancer. Except for local recurrence, women in their 20s and 30s had higher all-cause and cancer-specific mortality and progression rates than those in their 40s. Before the age of 50 years, age at breast cancer diagnosis showed an inverse correlation with outcomes; that is, the younger the patient, the poorer the prognosis. Higher histological grade, higher stage, and unfavourable molecular subtype probably contributed to this. On closer inspection, the very young group had poorer prognosis than other groups among patients with stage II disease. Notwithstanding, BCS was recommended for patients with stage II disease, as it did not decrease overall survival in this group. Chemotherapy did not provide a significant improvement in the survival of very young patients.

Several studies recently reported that very young (aged less than 30 years) and young (30–40 years) patients accounted for about 20–25 per cent of patients with breast cancer aged less than 50 years[15,17]. In a retrospective review of 215 688 patients (aged 15–49 years) with stage 0–III breast cancer in the National Cancer Database (NCDB) from 2010 to 2015, Murphy and colleagues[17] noted that very young patients accounted for 2.3 per cent, the same as the present study from the TCR (2.3 per cent). In a study[15] of 30 793 Korean patients (aged 20–49 years) with stage I–III breast cancer in the Korean Breast Cancer Registry (KBCR) between 2003 and 2010, 2.6 per cent of the patients were reported to be very young. The percentages of high histological grade and triple-negative tumours in the very young groups in the NCDB (64.2 and 23.7 per cent respectively) and KBCR (47.0 and 29.8 per cent) were obviously larger than their counterparts in the TCR

Table 1 Univariable Cox regression analyses of age groups (20–50 years) for overall, cancer-specific, and disease-free survival, and local recurrence-free status in patients with breast cancer with respect to cancer stage at diagnosis

Tumour stage*	Age (years)	Overall survival		Cancer-specific survival		Disease-free survival		Local recurrence-free	
		Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
I	20.0–29.9	1.00 (reference)	0.103	1.00 (reference)	0.001	1.00 (reference)	0.003	1.00 (reference)	0.204
	30.0–39.9	0.98 (0.51, 1.88)	0.956	0.93 (0.47, 1.84)	0.827	0.98 (0.58, 1.63)	0.927	0.81 (0.43, 1.50)	0.494
	40.0–50.0	0.78 (0.41, 1.46)	0.429	0.58 (0.30, 1.14)	0.116	0.72 (0.44, 1.19)	0.195	0.68 (0.37, 1.25)	0.213
II	20.0–29.9	1.00 (reference)	< 0.001	1.00 (reference)	< 0.001	1.00 (reference)	< 0.001	1.00 (reference)	0.049
	30.0–39.9	0.62 (0.46, 0.83)	0.001	0.60 (0.44, 0.81)	0.001	0.72 (0.55, 0.96)	0.024	1.39 (0.79, 2.45)	0.249
	40.0–50.0	0.54 (0.41, 0.71)	< 0.001	0.49 (0.37, 0.65)	< 0.001	0.58 (0.45, 0.76)	< 0.001	1.12 (0.65, 1.95)	0.684
III	20.0–29.9	1.00 (reference)	0.481	1.00 (reference)	0.516	1.00 (reference)	0.308	1.00 (reference)	0.878
	30.0–39.9	1.45 (0.78, 2.67)	0.237	1.37 (0.74, 2.53)	0.314	1.23 (0.74, 2.04)	0.435	1.02 (0.49, 2.11)	0.964
	40.0–50.0	1.38 (0.76, 2.51)	0.294	1.27 (0.70, 2.31)	0.434	1.08 (0.65, 1.77)	0.769	0.95 (0.47, 1.93)	0.890

Values in parentheses are 95 per cent confidence intervals. *According to sixth edition of AJCC classification of breast cancer.

(42.8 and 18.1 per cent). Regarding surgery, the percentage of BCS in the very young group in the NCDB (22.9 per cent) was markedly lower than that in the TCR (62.4 per cent) and KBCR (65.4 per cent). The NCDB study[17] reported that the rate of mastectomy was higher than that of BCS, probably owing to patient preference and/or reluctance to undergo radiation therapy. Interestingly, the 10-year overall survival rate in the very young group in the KBCR was similar to that in the present study (81.8 per cent)[15]. The younger age group had a higher incidence of ER/PR negativity and triple-negative tumours than the older age group[24].

For cosmetic reasons and potential sequelae, young women with breast cancer have conventionally preferred BCS (lumpectomy with adjuvant radiotherapy), as reported in the present study, but concerns regarding recurrence and reduced survival might influence a patient's decision to undergo mastectomy[25,26]. Although BCS was associated with improved long-term survival in the present multivariable analysis, the association of BCS with overall, cancer-specific, or disease-free survival became non-significant when controlled for stage; BCS may be selected for patients with more limited disease.

Several studies investigating the trends in surgical management of breast cancer in the USA and Europe have highlighted that an increasing number of younger patients undergo mastectomy[27,28]. The rates of BCS in Asian settings have traditionally been very low compared with those in Europe and the USA[27,28]. The increased use of mastectomy in Asia has been reported in several studies[29,30]. This attitude is based on the increased incidence of tumour recurrence after BCS in young women with breast cancer. However, increased local recurrence does not necessarily indicate a low survival rate.

Based on a study conducted in 536 patients in the Netherlands, Bantema-Joppe and co-workers[31] concluded that, although the rate of local recurrence significantly affected the rate of distant metastases or death, the increased risk of local recurrence after BCS compared with mastectomy did not lead to worse distant metastasis or death rates in patients aged less than 40 years. Another study from the UK investigating 3024[16] women aged 18–40 years with breast cancer also reported that, despite the higher local recurrence rates for BCS, surgical type did not influence the rates of distant metastasis or overall survival in young patients with breast cancer. The results of the present study were very similar to these findings, except that BCS was associated with better overall and cancer-specific survival. Recently, a study[18] of 1331 young patients (aged under 40 years) with early breast cancer diagnosed between 1997 and 2010 reported that local control and overall prognosis improved significantly in patients who underwent BCS, especially after 2005, the year after trastuzumab was introduced into routine clinical practice. The prevalence of young women with breast cancer treated with mastectomy remains high in Asian countries, and patients who had BCS appear to have survival rates similar to those of patients who underwent mastectomy[29,32].

The present study showed that adjuvant chemotherapy was associated with less local recurrence and better overall and cancer-specific survival in the young group, but not among the very young. A pooled analysis of 480 patients aged 40 years or less demonstrated that younger patients with hormone receptor-positive tumours benefit less from adjuvant systemic chemotherapy than those with hormone receptor-negative tumours[33]. However, adjuvant chemotherapy appears to be a very important component of a successful treatment regimen in young women with ER-negative breast cancer[34]. Even in the neoadjuvant setting, the GeparTrio study[35] suggested that younger age is consistently associated with greater benefit from preoperative anthracycline–taxane-based chemotherapy. In patients with triple-negative tumours, the pathological complete response rates were as high as 57 per cent among those aged under 40 years and 34 per cent in those aged over 40 years.

Neoadjuvant chemotherapy for breast cancer has been advocated and popularized in recent decades. A study[36] of 315 264 patients with breast cancer registered in the NCDB in 2010–2015 showed significant increases in the administration of neoadjuvant chemotherapy in all biological subtypes, with the greatest increase in patients with TNBC and HER2-positive tumours. The present study (between 2004 and 2014) had comparable findings, and the rate of neoadjuvant chemotherapy (10.6 per cent) was lower than the 20.2 per cent reported in the abovementioned study, possibly because the proportion of chemotherapy administered as treatment for breast cancer in the neoadjuvant setting has increased since 2010; it is most commonly administered to patients with triple-negative breast cancer and HER2-positive tumours. It is worth mentioning that the overall chemotherapy rate in very young patients was lower, whereas the neoadjuvant therapy rate was higher, than those in older patients. Because of the occurrence of premature menopause and infertility following chemotherapy, younger women (aged under 40 years) with early-stage hormone receptor-positive breast cancer might refuse to undergo adjuvant chemotherapy or hormone therapy[37].

This study also indicated that very young patients with stage II disease had a poorer prognosis than those with stage III tumours. This finding was partially supported by the results of a

Table 2 Multivariable Cox regression analyses of impact of age, tumour, and treatment variables on overall, cancer-specific, disease-free survival, and local recurrence-free status in patients with breast cancer aged 20–50 years

	Overall survival		Cancer-specific survival		Disease-free survival		Local recurrence-free	
	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
Age (years)		< 0.001		< 0.001		< 0.001		0.174
20.0–29.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
30.0–39.9	0.80 (0.62, 1.02)	0.067	0.77 (0.60, 0.99)	0.043	0.89 (0.71, 1.11)	0.312	1.13 (0.79, 1.63)	0.510
40.0–50.0	0.68 (0.54, 0.86)	0.002	0.62 (0.48, 0.79)	< 0.001	0.72 (0.58, 0.89)	0.003	1.00 (0.70, 1.43)	0.986
Surgery type		< 0.001		< 0.001		0.040		< 0.001
BCS	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Mastectomy	1.52 (1.36, 1.70)		1.57 (1.39, 1.78)		1.11 (1.01, 1.22)		0.74 (0.64, 0.84)	
Laterality		0.430		0.414		0.069		0.018
Right	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Left	0.96 (0.88, 1.04)	0.313	0.95 (0.86, 1.04)	0.256	0.97 (0.90, 1.05)	0.449	1.02 (0.91, 1.13)	0.785
Not specified	1.37 (0.61, 3.06)	0.443	1.33 (0.55, 3.20)	0.529	1.97 (1.06, 3.68)	0.033	2.95 (1.39, 6.23)	0.005
Tumour behaviour		< 0.001		< 0.001		< 0.001		< 0.001
Carcinoma *in situ* coexisted	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Invasive	2.85 (1.67, 4.86)		6.15 (2.54, 14.88)		3.01 (1.99, 4.57)		2.55 (1.61, 4.05)	
Differentiation		< 0.001		< 0.001		< 0.001		0.012
Well or moderate	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Poor or none	1.38 (1.25, 1.52)	< 0.001	1.45 (1.30, 1.61)	< 0.001	1.32 (1.21, 1.45)	< 0.001	1.22 (1.06, 1.39)	0.005
Not specified	1.06 (0.90, 1.25)	0.455	1.09 (0.91, 1.30)	0.361	1.10 (0.95, 1.27)	0.189	0.99 (0.80, 1.21)	0.881
Resection margin		< 0.001		< 0.001		< 0.001		< 0.001
Positive	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Negative	0.71 (0.61, 0.82)	< 0.001	0.66 (0.56, 0.77)	< 0.001	0.44 (0.39, 0.49)	< 0.001	0.38 (0.33, 0.44)	< 0.001
Unspecified	0.74 (0.63, 0.88)	0.001	0.69 (0.58, 0.83)	< 0.001	0.44 (0.38, 0.51)	< 0.001	0.2 (0.16, 0.25)	< 0.001
Co-morbidity		< 0.001		< 0.001		< 0.001		0.073
0	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
1	1.02 (0.88, 1.17)	0.841	0.99 (0.85, 1.16)	0.926	0.97 (0.85, 1.10)	0.586	0.88 (0.73, 1.06)	0.183
> 2	1.69 (1.47, 1.93)	< 0.001	1.50 (1.28, 1.75)	< 0.001	1.41 (1.23, 1.60)	< 0.001	1.24 (1.02, 1.51)	0.033
Not specified	0 (0, > 100)	0.900	0 (0, > 100)	0.916	0 (0, > 100)	0.870	0 (0, > 100)	0.907
Location		0.223		0.143		0.035		0.420
Lateral, superior quadrant	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Medial, upper quadrant	1.13 (0.99, 1.30)	0.074	1.10 (0.95, 1.28)	0.206	1.11 (0.98, 1.25)	0.094	1.15 (0.97, 1.37)	0.104
Central breast and nipple	1.01 (0.85, 1.20)	0.951	0.90 (0.74, 1.09)	0.294	0.89 (0.76, 1.05)	0.168	1.00 (0.80, 1.25)	0.989
Inferior breast	1.02 (0.89, 1.17)	0.800	0.99 (0.85, 1.15)	0.867	0.99 (0.87, 1.12)	0.820	1.08 (0.91, 1.29)	0.375
Overriding/ unknown	1.11 (0.99, 1.23)	0.064	1.10 (0.98, 1.23)	0.094	1.10 (1.00, 1.21)	0.057	1.11 (0.96, 1.27)	0.152
TNM stage*		< 0.001		< 0.001		< 0.001		< 0.001
I	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
II	2.01 (1.78, 2.27)	< 0.001	2.29 (2.00, 2.63)	< 0.001	1.77 (1.60, 1.95)	< 0.001	1.33 (1.16, 1.52)	< 0.001
III	6.12 (5.30, 7.06)	< 0.001	7.45 (6.35, 8.74)	< 0.001	6.33 (5.59, 7.17)	< 0.001	6.22 (5.24, 7.39)	< 0.001
Radiotherapy		0.274		0.170		< 0.001		< 0.001
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.95 (0.86, 1.04)		0.93 (0.84, 1.03)		0.71 (0.65, 0.77)		0.47 (0.41, 0.53)	
Chemotherapy/ immunotherapy		0.727		0.271		< 0.001		< 0.001
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	1.02 (0.90 , 1.16)		1.09 (0.94, 1.25)		0.75 (0.68, 0.83)		0.55 (0.48, 0.62)	
Hormone therapy		0.001		0.004		0.002		< 0.001
No	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Yes	0.83 (0.74, 0.93)		0.84 (0.75, 0.95)		0.84 (0.76, 0.94)		0.69 (0.59, 0.81)	
Molecular subtype		< 0.001		< 0.001		< 0.001		< 0.001
Luminal A	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Luminal B	1.52 (1.16, 2.00)	0.003	1.64 (1.21, 2.22)	0.002	1.46 (1.20, 1.78)	< 0.001	1.55 (1.22, 1.98)	< 0.001
HER2/*neu* type	1.87 (1.29, 2.72)	0.001	2.26 (1.52, 3.36)	< 0.001	1.52 (1.13, 2.05)	0.005	1.08 (0.73, 1.61)	0.686
Basal (triple-negative)	3.74 (2.77, 5.05)	< 0.001	4.13 (2.96, 5.75)	< 0.001	2.33 (1.82, 2.98)	< 0.001	1.81 (1.32, 2.48)	< 0.001
Not specified	2.02 (1.63, 2.52)	< 0.001	2.16 (1.68, 2.77)	< 0.001	1.04 (0.89, 1.21)	0.650	0.36 (0.29, 0.44)	< 0.001

Values in parentheses are 95 per cent confidence intervals. *According to sixth edition of AJCC classification of breast cancer. BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2.

study by Fu and colleagues[38]. Their stratified analysis indicated that differences in cancer-specific survival in younger patients compared with those aged under 40 years were worse for earlier-stage disease. The only difference between their results and the present findings was that this was not observed in patients with stage I disease. Although worse outcome has been noted in younger patients, drugs that specifically target cancer cells with genetic alterations that inhibit DNA repair are already being used in the clinical setting and may improve the long-term outcomes of patients with cancer[39].

Table 3 Multivariable Cox regression analyses of impact of surgery type and adjuvant therapies in patients with breast cancer according to patient age

	Overall survival		Cancer-specific survival		Disease-free survival		Local recurrence-free	
	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P	Hazard ratio	P
Age 20.0–29.9 years								
Surgery type (mastectomy *versus* BCS)								
Stage I	7.35 (0.99, 54.69)	0.051	4.65 (0.54, 40.27)	0.163	0.55 (0.13, 2.42)	0.430	0 (0, > 100)	0.934
Stage II	1.43 (0.76, 2.70)	0.272	1.43 (0.73, 2.77)	0.296	1.29 (0.68, 2.43)	0.439	0.32 (0.07, 1.46)	0.141
Stage III	1.46 (0.21, 10.26)	0.704	1.46 (0.21, 10.26)	0.704	1.14 (0.25, 5.16)	0.868	0.89 (0.07, 11.88)	0.927
Chemotherapy (yes *versus* no)								
Stage I	0.37 (0.05, 2.66)	0.322	0.46 (0.06, 3.62)	0.461	0.60 (0.11, 3.49)	0.573	0.13 (0.00, 3.94)	0.238
Stage II	0.92 (0.48, 1.76)	0.799	0.96 (0.49, 1.88)	0.903	1.08 (0.58, 2.02)	0.808	0.64 (0.12, 3.42)	0.602
Stage III	10.79 (2.20, 52.81)	0.003	10.79 (2.20, 52.81)	0.003	6.23 (1.68, 23.13)	0.006	0.78 (0.07, 8.39)	0.839
Radiotherapy (yes *versus* no)								
Stage I	0.53 (0.12, 2.40)	0.408	0.52 (0.11, 2.57)	0.422	0.15 (0.05, 0.50)	0.002	0 (0, > 100)	0.908
Stage II	1.21 (0.64, 2.31)	0.555	1.26 (0.64, 2.48)	0.499	0.91 (0.49, 1.69)	0.756	0.14 (0.03, 0.72)	0.018
Stage III	0.45 (0.07, 3.17)	0.426	0.45 (0.07, 3.17)	0.426	0.26 (0.07, 0.95)	0.042	0.34 (0.07, 1.71)	0.190
Hormone therapy (yes *versus* no)								
Stage I	1.33 (0.28, 6.28)	0.717	2.18 (0.40, 12.01)	0.370	0.96 (0.33, 2.77)	0.932	0.35 (0.06, 2.04)	0.244
Stage II	1.23 (0.64, 2.34)	0.532	1.19 (0.61, 2.33)	0.607	0.91 (0.49, 1.69)	0.759	0.36 (0.10, 1.31)	0.121
Stage III	1.91 (0.36, 10.09)	0.445	1.91 (0.36, 10.09)	0.445	1.80 (0.51, 6.40)	0.361	0.91 (0.18, 4.69)	0.906
Age 30.0–39.9 years								
Surgery type (mastectomy *versus* BCS)								
Stage I	0.94 (0.58, 1.52)	0.797	0.91 (0.54, 1.52)	0.713	0.52 (0.36, 0.75)	< 0.001	0.35 (0.22, 0.58)	< 0.001
Stage II	1.58 (1.20, 2.08)	0.001	1.62 (1.21, 2.18)	0.001	1.10 (0.86, 1.40)	0.435	0.68 (0.48, 0.97)	0.035
Stage III	1.76 (1.06, 2.92)	0.029	1.74 (1.03, 2.92)	0.038	1.57 (1.00, 2.45)	0.048	1.69 (0.85, 3.37)	0.133
Chemotherapy (yes *versus* no)								
Stage I	1.11 (0.71, 1.73)	0.651	1.16 (0.72, 1.87)	0.538	0.61 (0.40, 0.91)	0.017	0.22 (0.11, 0.43)	< 0.001
Stage II	1.57 (1.23, 2.00)	< 0.001	1.57 (1.21, 2.03)	0.001	1.00 (0.79, 1.27)	0.987	0.31 (0.20, 0.47)	< 0.001
Stage III	1.61 (1.13, 2.29)	0.008	1.63 (1.13, 2.34)	0.008	1.13 (0.80, 1.59)	0.485	0.29 (0.14, 0.60)	0.001
Radiotherapy (yes *versus* no)								
Stage I	0.46 (0.28, 0.74)	0.001	0.36 (0.21, 0.61)	< 0.001	0.24 (0.17, 0.35)	< 0.001	0.21 (0.13, 0.34)	< 0.001
Stage II	0.93 (0.72, 1.20)	0.579	0.87 (0.67, 1.14)	0.312	0.65 (0.52, 0.82)	< 0.001	0.46 (0.32, 0.66)	< 0.001
Stage III	0.65 (0.46, 0.92)	0.015	0.66 (0.46, 0.94)	0.022	0.59 (0.43, 0.81)	0.001	0.43 (0.27, 0.69)	< 0.001
Hormone therapy (yes *versus* no)								
Stage I	0.85 (0.52, 1.39)	0.509	0.77 (0.45, 1.29)	0.313	1.00 (0.66, 1.52)	0.994	1.21 (0.67, 2.20)	0.522
Stage II	0.76 (0.58, 1.00)	0.051	0.81 (0.60, 1.08)	0.143	0.95 (0.74, 1.23)	0.711	0.81 (0.56, 1.17)	0.265
Stage III	0.63 (0.44, 0.90)	0.012	0.62 (0.43, 0.90)	0.012	0.62 (0.45, 0.87)	0.005	0.44 (0.27, 0.72)	0.001
Age 40.0–50.0 years								
Surgery type (mastectomy *versus* BCS)								
Stage I	0.93 (0.67, 1.29)	0.652	0.87 (0.58, 1.29)	0.481	0.41 (0.32, 0.52)	< 0.001	0.31 (0.23, 0.41)	< 0.001
Stage II	1.67 (1.40, 2.00)	< 0.001	1.77 (1.46, 2.15)	< 0.001	1.23 (1.05, 1.44)	0.011	0.69 (0.55, 0.86)	0.001
Stage III	1.97 (1.38, 2.82)	< 0.001	2.23 (1.50, 3.30)	< 0.001	1.67 (1.22, 2.30)	0.001	1.40 (0.90, 2.15)	0.133
Chemotherapy (yes *versus* no)								
Stage I	1.49 (1.13, 1.95)	0.004	1.56 (1.13, 2.16)	0.007	0.65 (0.50, 0.85)	0.002	0.19 (0.13, 0.29)	< 0.001
Stage II	1.15 (0.99, 1.34)	0.071	1.22 (1.04, 1.44)	0.017	0.90 (0.78, 1.05)	0.187	0.28 (0.22, 0.37)	< 0.001
Stage III	1.11 (0.89, 1.38)	0.363	1.16 (0.93, 1.46)	0.197	0.90 (0.72, 1.12)	0.337	0.21 (0.13, 0.35)	< 0.001
Radiotherapy (yes *versus* no)								
Stage I	0.75 (0.54, 1.03)	0.079	0.79 (0.53, 1.18)	0.247	0.35 (0.28, 0.45)	< 0.001	0.25 (0.19, 0.33)	< 0.001
Stage II	1.17 (1.01, 1.37)	0.041	1.22 (1.04, 1.44)	0.018	0.97 (0.84, 1.12)	0.661	0.66 (0.53, 0.83)	< 0.001
Stage III	0.74 (0.60, 0.90)	0.003	0.71 (0.57, 0.87)	0.001	0.61 (0.51, 0.74)	< 0.001	0.53 (0.40, 0.70)	< 0.001
Hormone therapy (yes *versus* no)								
Stage I	0.73 (0.53, 1.00)	0.051	0.74 (0.51, 1.08)	0.117	0.77 (0.59, 1.01)	0.061	0.81 (0.58, 1.15)	0.244
Stage II	0.71 (0.60, 0.83)	< 0.001	0.67 (0.56, 0.79)	< 0.001	0.76 (0.65, 0.89)	< 0.001	0.78 (0.62, 0.99)	0.041
Stage III	0.68 (0.55, 0.84)	< 0.001	0.73 (0.58, 0.91)	0.006	0.80 (0.65, 0.98)	0.035	0.65 (0.48, 0.88)	0.005

Values in parentheses are 95 per cent confidence intervals. Tumours were staged according to sixth edition of AJCC classification of breast cancer. Estimates were adjusted for breast laterality, tumour cell grade, tumour behaviour, co-morbidity, and tumour location. BCS, breast-conserving surgery.

The major strengths of this study are the population-based design and large study population with complete follow-up data, making the results generally applicable. Data regarding death date and causes of death were primarily obtained from the Death Registry, not solely from the TCR, to avoid missing data or outdated information. Furthermore, the data were registered and regularly updated in the TCR by well trained registrars using a standardized coding manual.

The present results should be interpreted with consideration of some limitations. First, the analyses of tumour laterality, histological grade, tumour size, location, resection margin, and molecular subtype were limited by missing data for some tumours. In addition, the registry had no data on ER and PR status from 2007 to 2009, although this information might be important for the prognosis of patients with breast cancer. To overcome this, data on administration of hormone therapy agents (tamoxifen,

letrozole, exemestane, and anastrozole) for individual patients were used as surrogate data.

Second, many patients had no data on HER2/*neu* status as the TCR did not provide this information until 2011, let alone information on genetic (*BRCA1/2*) mutation testing, which was likely to be more common in the younger groups . In addition, Olaparib, a poly-ADP-ribose polymerase (PARP) inhibitor, has been reimbursed by the National Health Insurance for patients with terminal TNBC whose genetic assay indicates *BRCA1/2* mutation only since November 2020. PARP inhibitor offers a promising role either combined with or without other agents to combat cell proliferation in *BRCA1/2* mutation tumours[40]. Therefore, it was not possible to control for the tumour characteristics with HER2/*neu*, *BRCA* mutation, and use of a PARP inhibitor in the multivariable survival analyses owing to a large amount of unknown data.

Third, the effect of chemotherapy in very young patients with stage III disease cannot be overexaggerated as the sample size was only 56. Fourth, the age definition of 'very young' is arbitrary. It was not possible to determine whether the age of 30 years was the best cut-off value. However, classifying patients as very young or young needs to be explored further. Other classifications of patients should not be overlooked. Finally, the TCR is a national cancer registry that records only 85 per cent of all patients with newly diagnosed cancer annually in Taiwan.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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