Clinical and Experimental Medicine (2025) 25:92
https://doi.org/10.1007/s10238-025-01621-2

RESEARCH

The necessity of adjuvant chemotherapy in young patients with $T_1N_0M_0$ breast cancer: a population-based study

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Received: 25 January 2025 / Accepted: 27 February 2025

Abstract

Chemotherapy clearly adversely affects fertility in women of childbearing age. But it is not yet clear whether chemotherapy at the expense of fertility can benefit younger patients with early-stage breast cancer. We conducted a retrospective cohort study utilizing the Surveillance, Epidemiology, and End Results database and the Shanghai Jiao Tong University Breast Cancer Data Base spanning from 2010 to 2020 to investigate early-stage breast malignant carcinoma in patients aged between 20 and 39 years. To address covariate imbalance, propensity score matching (PSM) was employed with a ratio of 1:1 and caliper set at 0.02 standard deviation of propensity score. Univariate and multivariate analyses were performed to evaluate the impact of chemotherapy on both breast cancer-specific survival (BCSS) and overall survival (OS). We identified a total of 6265 patients with complete information about breast cancer. Among them, 3855 patients received chemotherapy. Following successful PSM, we obtained a matched cohort comprising 3038 patients where the characteristics between the two groups were balanced except for race. Kaplan–Meier survival analysis revealed no significant differences in BCSS ($P=0.183$) and OS ($P=0.295$) between the chemotherapy group and no-chemotherapy group. Similarly, in matched dataset. multivariate COX analysis revealed that chemotherapy did not significantly reduce the risk of BCSS (HR 1.332; 95% CI [0.865–2.051], $P=0.193$) and OS (HR 1.225; 95% CI [0.818–1.833], $P=0.324$). The chemotherapy group did not demonstrate a superior benefit in any of the subgroups when stratified analyses were conducted based on molecular subtype, tumor size, age, and ethnicity. Chemotherapy fails to significantly improve prognostic outcomes in young patients diagnosed with early-stage breast cancer. With the help of genetic testing, these patients can expect further step-down therapy in the future.

Keywords Young · Breast cancer · Chemotherapy · Breast cancer-specific survival · SEER database

Background

Despite significant advancements in anti-breast cancer research and treatment, breast cancer remains a substantial public health concern. According to statistics from 2010 to 2019 in the USA, there has been an annual increase of 0.5% in the incidence of breast cancer [1]. Globally, it is estimated that there will be 2.3 million new cases of breast cancer in 2022, making it the second most common type of cancer and the leading cause of cancer-related deaths among women [2]. As the incidence of breast cancer continues to rise, so does its prevalence among young women. In developed countries, approximately 5–7% of breast cancer patients are under the age of 40 years [3], while this percentage can reach as high as 10–20% in developing countries [4, 5].

Many previous studies have identified young age at diagnosis as an independent risk factor influencing the risk of breast cancer recurrence [6, 7]. Younger women with breast cancer tend to have larger tumors, later stages, and a higher proportion of aggressive tumor subtypes such as triple-negative and HER2 overexpression subtypes compared to older women [8, 9]. Therefore, in younger patients, physicians tend to use more aggressive treatments and hope that

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Published online: 20 March 2025

this will reduce the risk of recurrence and death [10, 11]. However, the toxicity of chemotherapy can affect a woman's fertility by destroying the ovarian follicles that make up her ovum reserve [12]. Although there are many well-established methods to preserve patients' fertility [13], many women of reproductive age are still infertile due to antitumor therapy, which seriously affects their quality of life [14].

To mitigate the toxic side effects of chemotherapy, the guideline excludes certain early-stage breast cancer patients with tumors smaller than 1 cm in diameter and negative lymph node status from chemotherapy based on available research evidence indicating no impact on tumor prognosis [15]. Consequently, there is a potential opportunity to spare young patients with early-stage breast cancer from chemotherapy while ensuring disease survival and optimizing fertility preservation. Several studies suggest that lymph node status, estrogen receptor status and molecular subtype of the tumor are robust predictors of disease recurrence. Therefore, adjuvant treatment regimens should be guided by these factors rather than solely relying on age of onset [16, 17].

To comprehensively address this uncertainty, we conducted an analysis using the Surveillance, Epidemiology, and End Results (SEER) database and the Shanghai Jiao Tong University Breast Cancer Data Base (SJTUBCDB) spanning from 2010 to 2020 to evaluate the efficacy of chemotherapy in young patients diagnosed with early breast cancer. Subgroup analyses were performed considering different age groups, tumor size categories, and molecular subtypes to explore the feasibility of exemption from chemotherapy for young early-stage breast cancer patients.

Methods

This was a retrospective cohort study using the SEER database and SJTUBCDB. The study used data from 2010 to 2020 to assess breast cancer-specific survival (BCSS) and overall survival (OS) in young breast cancer patients with chemotherapy and early stage without chemotherapy.

Data sources and patient selection

Patient data were obtained from the SEER database using SEER*Stat software. The SEER database contains approximately 28% of all tumor cases in the USA. SJTUBCDB is a breast cancer database established by Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine. It has included more than 96,000 breast cancer cases from 43 breast cancer treatment centers in China. No patient informed consent or institutional ethical review was required for this study because the database was publicly available and we obtained permission from both data for the use of the data. Inclusion criteria were as follows (1) women between 20 and 39 years of age; (2) Pathologic diagnosis of malignant tumor of the breast is invasive ductal carcinoma, code 8500; (3) no neoadjuvant therapy before surgical treatment; (4) systemic therapy after surgery; (5) no distant metastasis according to the 8th edition of the AJCC Breast Cancer Criteria: T-stage ≤ 1, N-stage ≤ 0; (6) only one malignancy was obtained. Exclusion criteria were (1) diagnosis of bilateral breast cancer; (2) lack of key information such as race, marital status, histologic grading, lymph node status, and molecular subtype; and (3) death or loss to follow-up within 6 months of diagnosis.

Outcome indicators

Patients were categorized into chemotherapy and non-chemotherapy groups based on chemotherapy recoding in the database. BCSS was the first endpoint of the study, and OS was the second endpoint of the study. BCSS was defined as the time from the diagnosis of breast cancer to death due to breast cancer. OS was defined as the time from the diagnosis of breast cancer to death or at the time of the last follow-up visit. The follow-up period was from January 1, 2010 to December 31, 2020. For patients who are alive at the end of the follow-up period, the time from disease diagnosis to the end of the study will be considered their follow-up time. The follow-up time for patients lost to follow-up will be calculated from disease diagnosis until the last contact.

Statistical analysis

Demographic and clinical characteristics of chemotherapy and non-chemotherapy cases in the whole cohort and the 1:1 propensity score matched (PSM) group were analyzed using Chi-square tests. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards regression modeling to identify factors associated with outcomes. Variables that showed a significance level of $P < 0.05$ in univariate analysis were included as candidates for multivariate analysis. The proportional hazards hypothesis was evaluated using the Schoenfeld residual test. To reduce baseline differences in demographic and clinical characteristics, patients in the chemotherapy and non-chemotherapy groups were matched one-to-one by PSM methods, with age, race, marital status, grading, AJCC T-stage, ER status, PR status, HER2 status, surgical modality, and radiotherapy status as matching covariates. A nearest neighbor matching method with a caliper distance of 0.02 was used for this purpose. Survival curves were generated using the Kaplan–Meier method, whereas the statistical significance of the difference in BCSS and OS between patients who received chemotherapy and those who did not was determined by the log-rank test. Statistical analysis was

Table 1 Baseline characteristics of patients with chemotherapy and no-chemotherapy

		SEER data				χ^2	P^c	SJTU data				χ^2/F	P^c
		Total		No-Chem-otherapy	Chemotherapy			Total		No-Chem-otherapy	Chemotherapy		
Age	20–24	93	1.53%	24	69	100.739	< 0.001	2	1.10%	1	1	2.368*	0.504*
	25–29	490	8.05%	132	358			10	5.52%	2	8		
	30–34	1573	25.85%	500	1073			57	31.49%	21	36		
	35–39	3928	64.56%	1698	2230			112	61.88%	32	80		
Race	White	4443	73.03%	1690	2753	15.3	< 0.001						
	Black	690	11.34%	245	445								
	Other[a]	951	15.63%	419	532			181	100.00%	56	125		
Marital status	Married	3738	61.44%	1403	2335	9.446	0.009	112	61.88%	37	75	0.604	0.437
	Not married[b]	2122	34.88%	3792	1570			69	38.12%	19	50		
	Unknown	224	3.68%	77	147								
Grade	I	520	8.55%	358	162	443.854	< 0.001	20	11.05%	12	8	20.437	< 0.001
	II	2575	42.32%	1196	1379			113	62.43%	40	73		
	III&IV	2989	49.13%	800	2189			48	26.52%	4	44		
Tumor size	T1a	630	10.36%	415	215	334.437	< 0.001	47	25.97%	22	25	8.774*	0.009*
	T1b	149	2.45%	116	33			128	70.72%	34	94		
	T1c	5305	87.20%	1823	3482			6	3.31%	0	6		
Subtype	HR−/HER2−	776	12.75%	17	759	1415.577	< 0.001	20	11.05%	0	20	30.709*	< 0.001*
	HR−/HER2+	304	5.00%	14	290			16	8.84%	1	15		
	HR+/HER2−	4055	66.65%	2241	1814			118	65.19%	52	66		
	HR+/HER2+	949	15.60%	82	867			27	14.92%	3	24		
Surgery	Mastectomy	1545	25.39%	576	969	9.073	0.011	74	40.88%	23	51	0.215*	1*
	Partial mastectomy	2409	39.60%	988	1421			102	56.35%	32	70		
	Reconstruction	2130	35.01%	790	1340			5	2.76%	1	4		
Radiotherapy	Yes	2285	37.56%	1000	1285	39.686	< 0.001	78	43.09%	20	58	1.801	0.197
	No/unknown	3799	62.44%	1354	2445			103	56.91%	36	67		

[a]Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown

[b]Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed

[c]The *P* value was calculated between the chemotherapy and no-chemotherapy groups, and bold type indicates significance

*Fisher's precise test

Table 2 Multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS) and overall survival (OS) in all patients

		BCSS		OS	
		HR (95%CI)	*P*	HR (95%CI)	*P*
Age	20–24	Reference	0.25	Reference	0.497
	25–29	0.494 (0.163–1.497)	0.212	0.567 (0.19–1.693)	0.31
	30–34	0.430 (0.152–1.212)	0.11	0.543 (0.194–1.519)	0.245
	35–39	0.381 (0.138–1.057)	0.064	0.485 (0.176–1.336)	0.162
Race	White	Reference	0.001	Reference	0.023
	Black	1.912 (1.236–2.958)	0.004	1.542 (1.018–2.335)	0.041
	Other[a]	1.763 (1.194–2.602)	0.004	1.519 (1.048–2.203)	0.027
Marital status	Married	Reference	0.017	Reference	0.328
	Not married[b]	0.615 (0.428–0.885)	0.009	0.804 (0.583–1.110)	0.184
Grade	I	Reference	0.23	Reference	0.284
	II	1.627 (0.661–4.004)	0.289	0.992 (0.494–1.994)	0.983
	III&IV	1.927 (0.806–4.826)	0.137	1.278 (0.641–2.548)	0.486
Tumor status	T1a	Reference	0.561	Reference	0.525
	T1b	2.236 (0.497–10.055)	0.294	1.431 (0.35–5.849)	0.618
	T1c	1.210 (0.640–2.287)	0.557	1.439 (0.767–2.702)	0.257
Subtype	HR-/HER2-	Reference	0.002	Reference	< 0.001
	HR-/HER2+	0.397 (0.167–0.946)	0.037	0.337 (0.143–0.793)	0.013
	HR+/HER2-	0.688 (0.457,1.035)	0.073	0.645 (0.444–0.938)	0.022
	HR+/HER2+	0.330 (0.180–0.603)	< 0.001	0.313 (0.178–0.548)	< 0.001
Surgery	Mastectomy	Reference	0.452	Reference	0.293
	Partial mastectomy	0.759 (0.445–1.295)	0.311	0.779 (0.475–1.277)	0.321
	Reconstruction	0.807 (0.546–1.194)	0.284	0.759 (0.528–1.092)	0.137
Radiotherapy	No/unknown	Reference	0.871	Reference	0.655
	Yes	0.959 (0.581–1.584)		0.899 (0.562–1.436)	
Chemotherapy	No	Reference	0.021	Reference	0.023
	Yes	1.619 (1.076–2.436)		1.549 (1.061–2.262)	

[a]Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown

[b]Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed

performed using SPSS software version 26. *P* values less than 0.05 indicated statistical significance.

Results

Patient demographics and tumor characteristics

A total of 6265 patients met the enrollment criteria, with 3855 receiving postoperative chemotherapy and 2410 not receiving it. The median follow-up time was 82 months. Table 1 shows the demographic and clinical characteristics of the chemotherapy and non-chemotherapy groups. The age distribution, molecular staging distribution, and proportion of cases treated with radiotherapy were close in both databases, with *p* values of 0.266, 0.131, and 0.139, respectively. The SEER database had the highest proportion of grade III and T1c cases, whereas the SJTU database had the highest proportion of grade II and T1b cases. More patients underwent breast reconstruction surgery in the USA, while more patients underwent breast-conserving surgery in China. Within the database, there were also clear differences in case characteristics between the chemotherapy and non-chemotherapy groups, implying that physicians in both the USA and China have certain criteria for determining whether or not to administer chemotherapy.

Comparison of survival between chemotherapy group and no-chemotherapy group

Because of the large number of cases in the SEER database, the results of the multifactorial statistical analysis of the two groups of patients in the SEER database using COX regression are presented in Table 2. Both BCSS and OS

Table 3 Baseline characteristics of patients with chemotherapy and no-chemotherapy in PSM group

		Total		No-Chemotherapy		Chemotherapy		$\chi 2$	P[c]
Age	20–24	42	1.38%	22	0.73%	20	0.66%	2.792	0.425
	25–29	226	7.44%	105	3.47%	121	3.98%		
	30–34	783	25.77%	379	12.52%	404	13.30%		
	35–39	1987	65.40%	1013	33.45%	974	32.06%		
Race	White	2208	72.68%	1123	37.09%	1085	35.71%	7.517	0.023
	Black	314	10.34%	134	4.43%	180	5.92%		
	Other[a]	516	16.98%	262	8.65%	254	8.36%		
Marital status	Married	1891	62.24%	953	31.47%	938	30.88%	2.875	0.237
	Not married[b]	1042	34.30%	522	17.24%	520	17.12%		
	Unknown	105	3.46%	44	1.45%	61	2.01%		
Grade	I	92	3.03%	35	1.16%	57	1.88%	5.791	0.055
	II	1755	57.77%	876	28.93%	879	28.93%		
	III&IV	1191	39.20%	608	20.08%	583	19.19%		
Tumor status	T1a	198	6.52%	105	3.47%	93	3.06%	1.756	0.416
	T1b	9	0.30%	3	0.10%	6	0.20%		
	T1c	2831	93.19%	1411	46.60%	1420	46.74%		
Subtype	HR-/HER2-	33	1.09%	17	0.56%	16	0.53%	0.189	0.979
	HR-/HER2+	30	0.99%	14	0.46%	16	0.53%		
	HR+/HER2-	2815	92.66%	1407	46.47%	1408	46.35%		
	HR+/HER2+	160	5.27%	82	2.71%	79	2.60%		
Surgery	Mastectomy	815	26.83%	410	13.54%	405	13.33%	3.758	0.153
	Partial mastectomy	1146	37.72%	549	18.13%	597	19.65%		
	Reconstruction	1077	35.45%	560	18.49%	517	17.02%		
Radiotherapy	Yes	1122	36.93%	551	18.20%	571	18.80%	0.565	0.452
	No/unknown	1916	63.07%	968	31.97%	948	31.20%		

[a]Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown

[b]Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed

[c]The *P* value of the Chi-square test was calculated between the chemotherapy and no-chemotherapy groups, and bold type indicates significance

were influenced by race and molecular subtype factors. Both BCSS and OS were influenced by ethnicity and molecular subtype as factors. Marital status only showed significant differences in BCSS. Conversely, tumor size, histological grading, surgical approach, and the presence or absence of radiotherapy had no significant impact on prognosis. To ensure comparability between the two groups, a 1:1 propensity-matched analysis was conducted with a caliper value of 0.02 resulting in 1519 matched pairs out of 6084 patients. A Chi-square test was performed on the matched dataset (Table 3), demonstrating that apart from a slight difference in ethnic composition percentage, all other influences were well balanced between the two patient groups. Subsequently, another multifactorial statistical analysis using COX regression was conducted on the matched dataset which revealed that age and ethnicity were independently associated with the risk of tumor-related death in patients regardless of their OS. Chemotherapy did not improve BCSS or OS in early-stage breast cancer patients (Table 4).

Survival analysis in propensity score matched

Kaplan–Meier survival analyses of the SEER dataset and the SJTU dataset showed that patients in the chemotherapy group did not show an advantage in BCSS and OS. Even in the SEER dataset, patients in the non-chemotherapy group gained an advantage in BCSS and OS before PSM (Fig. 1). In the SJTU dataset, 4 of 56 patients who did not receive chemotherapy experienced a recurrence, 7 of 125 patients who received chemotherapy experienced a recurrence, and 1 of these patients died of breast cancer recurrence. The analysis of invasive disease-free survival and BCSS/OS did not show statistical differences, with *P* values of 0.601 and 0.497, respectively.

According to current guidelines, adjuvant treatment options for early breast cancer are recommended based on tumor size and molecular subtype. Therefore, we stratified these two factors separately using paired patient data and conducted Kaplan–Meier survival analyses with BCSS and

Table 4 Multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS) and overall survival (OS) in PSM group

		BCSS		OS	
		HR (95%CI)	*P*	HR (95%CI)	*P*
Age	20–24	Reference	0.014	Reference	0.053
	25–29	1.364 (0.297–6.252)	0.69	1.274 (0.279–5.811)	0.754
	30–34	0.417 (0.092–1.887)	0.256	0.474 (0.107–2.104)	0.326
	35–39	0.600 (0.140–2.572)	0.492	0.677 (0.159–2.877)	0.598
Race	White	Reference	0.021	Reference	0.168
	Black	2.014 (1.101–3.682)	0.023	0.699 (0.424–1.150)	0.159
	Other[a]	1.726 (1.035–2.877)	0.036	1.101 (0.549–2.207)	0.786
Marital status	Married	Reference	0.061	Reference	0.526
	Not married[b]	0.615 (0.428–0.885)	0.028	0.771 (0.491–1.210)	0.258
	Unknown	0.455 (0.110–1.883)	0.277	0.954 (0.343–2.657)	0.929
Grade	I	Reference	0.425	Reference	0.101
	II	1.149 (0.278–4.755)	0.848	0.426 (0.181–1.001)	0.05
	III&IV	1.509 (0.364–6.261)	0.571	0.559 (0.237–1.319)	0.184
Tumor status	T1a	Reference	0.999	Reference	0.954
	T1b	0.000054 (9.8758E-228–2.977E+218)	0.97	0.000032 (1.678E-208–6.257E+198)	0.965
	T1c	0.986 (0.350–2.778)	0.979	1.171 (0.424–3.231)	0.76
Subtype	HR-/HER2-	Reference	0.994	Reference	0.987
	HR-/HER2+	0.672 (1.0385E-181–4.351E+180)	0.999	0.827 (1.3104E-174–5.219E+173)	0.999
	HR+/HER2-	19,078.313 (3.161E-123–1.303E+131)	0.947	19,495.176 (1.0284E-3.696E+130)	0.947
	HR+/HER2+	16,311.766 (2.7102E-123–1.116E+131)	0.948	15,905.626 (8.3765E-123–3.020E+130)	0.948
Surgery	Mastectomy	Reference	0.769	Reference	0.674
	Partial mastectomy	0.781 (0.383–1.593)	0.497	0.779 (0.475–1.277)	0.38
	Reconstruction	0.874 (0.505–1.512)	0.631	0.759 (0.528–1.092)	0.671
Radiotherapy	No/unknown	Reference	0.228	Reference	0.226
	Yes	1.493 (0.778–2.866)		1.479 (0.785–2.786)	
Chemotherapy	No	Reference	0.193	Reference	0.324
	Yes	1.332 (0.865–2.051)		1.225 (0.818–1.833)	

[a]Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown

[b]Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed

OS as endpoints (Figs. 2 and 3). Unfortunately, complete survival curves could not be obtained due to an insufficient number of events in certain subgroups. Nevertheless, based on current statistics, both T1a and T1c patients did not derive benefit from chemotherapy; HR+HER2− and HR+HER2+ patients also did not show any benefit from chemotherapy. Cox regression analysis of the post-PSM dataset identified age and ethnicity as two factors associated with BCSS among patients. Subsequently, Kaplan–Meier survival analyses were performed for these two factors stratified by BCSS as an endpoint (Figs. 4 and 5). The statistical analysis reveals a marginal advantage of the non-chemotherapy group over the chemotherapy group in terms of BCSS within both the 30- and 34-year-old subgroup and the white subgroup. However, no significant difference in BCSS was observed between the two groups in other subgroups.

Discussion

We used multicenter, large-scale data from the SEER database and the SJTU database to investigate whether young women with early-stage breast cancer can be spared from chemotherapy and to reduce the bias associated with small sample data from a single center. It is also possible to validate the findings of the databases against each other. The current definition of breast cancer in young women lacks consistency. Previous studies have defined "young women" as those below 35 years of age or categorized them into two groups: those under 40 years old versus those aged 40 and above, or used menopausal status as a surrogate [18, 19]. According to the European College of Oncology and the European Society for Medical Oncology, a "young woman" is defined as an individual younger than 40 years at the time

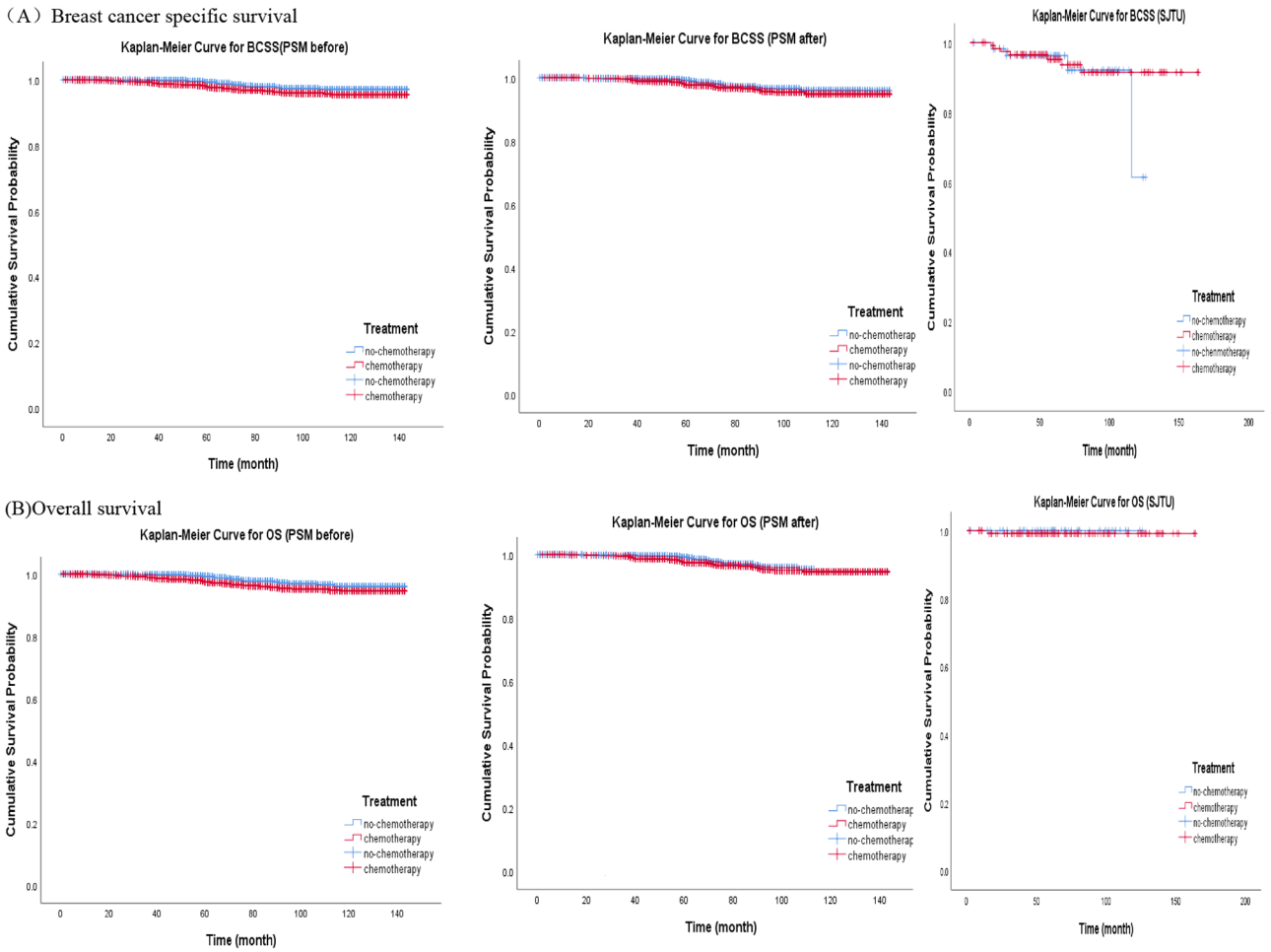

Fig. 1 Kaplan–Meier curves for patients' breast cancer (BC)-specific survival (**A**) and overall survival (**B**). The 95% confidence intervals (derived from simulated hazard estimates), the number of patients at risk at different time points, and the log-rank test for *P* are displayed on the graphs

of breast cancer diagnosis [20]. Considering that women often have high fertility intentions before reaching 40 years old and that chemotherapy significantly impacts their reproductive function, we selected a study population aged between 20 and 39 years by taking into account subgroups within the SEER database.

It has been suggested that younger women are a unique subgroup of breast cancer patients with poorer biological characteristics, such as poorly differentiated tumors, high Ki-67 expression, extensive lymph node metastasis, and a higher proportion of triple-negative and HER2+ tumors, compared to older women [6, 7]. However, the distribution of patients with different molecular subtypes in this study was very similar to the overall incidence of breast cancer in all age groups [1]. In addition, no overrepresentation of triple-negative and HER2+ tumors was observed. This discrepancy may be due to regional and demographic differences between the study cohorts. The data from the study by Prof. Fangjian Guo was obtained from only a sub-database of the SEER database [6]. The data from the study by Prof. Akemi Kataoka was obtained from patients in the Japanese region. From the data of this study, the target and range of income differed [7]. The meta-analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) age had little effect on the risk of recurrence reduced by chemotherapy [21].

Current guidelines do not differentiate adjuvant treatment options based on age, as treatment decisions are primarily guided by disease stage, biological characteristics, and patient preference. The guidelines delineate the specific circumstances under which exemption from chemotherapy may be considered [22]. However, in these same circumstances, young women often receive more aggressive treatment. This approach may result in excessive treatment and impaired fertility in specific patient populations. Subgroup survival analysis of this study demonstrated no improvement in BCSS and OS with chemotherapy across three dimensions: tumor size, molecular subtype, and ethnicity. Previous studies have shown that some young women achieve favorable

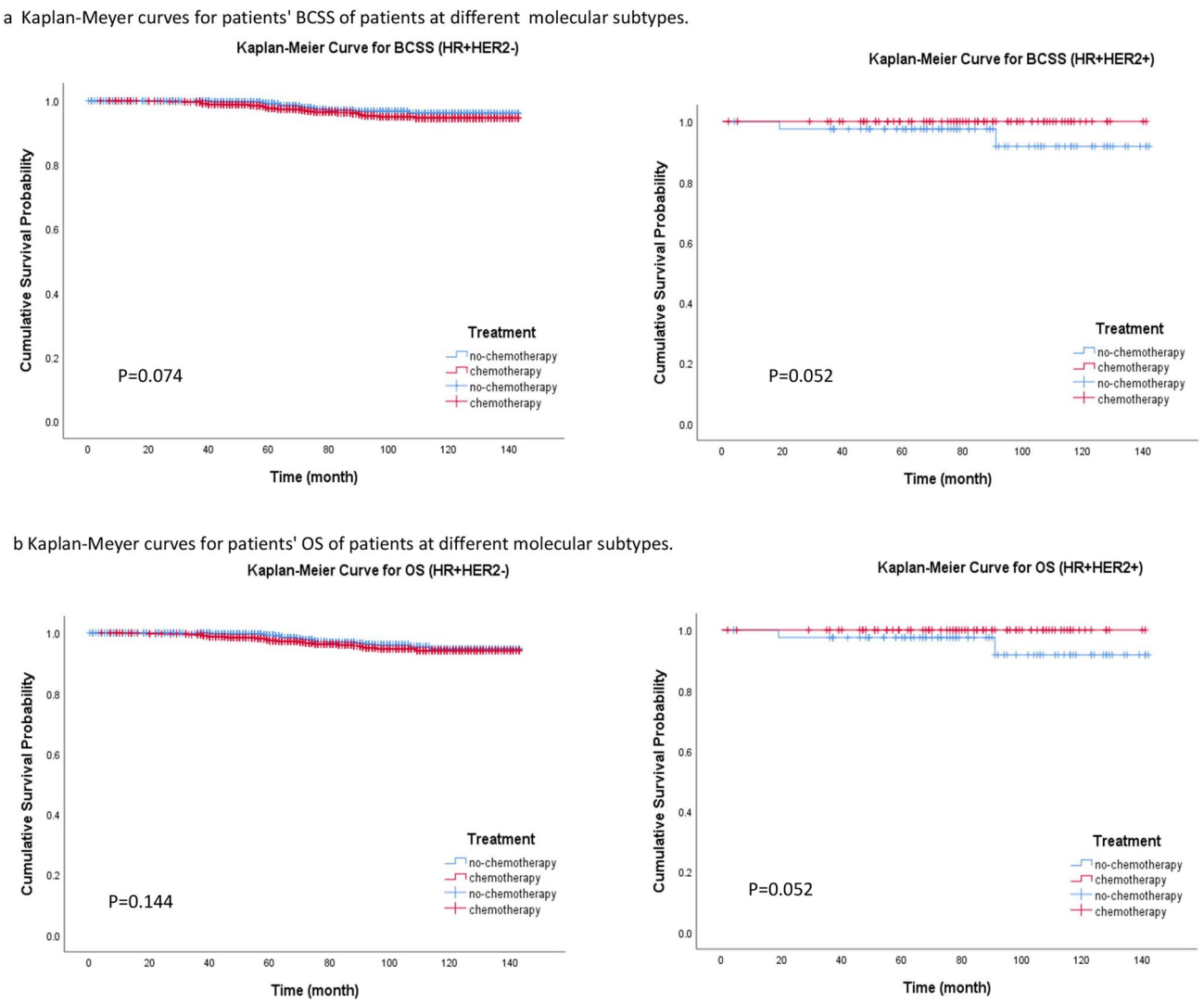

Fig. 2 **a** Kaplan–Meier curves for patients BCSS of patients at different molecular subtypes. **b** Kaplan–Meier curves for patients' OS of patients at different molecular subtypes. The log-rank test for P are displayed on the graphs

clinical outcomes with endocrine therapy alone [23]. Therefore, the decision to administer chemotherapy should not solely rely on age as an indicator; instead, greater consideration should be given to the pathological characteristics of the tumor [16, 17]. Currently available genetic testing tools can aid in identifying HR+HER2− breast cancers that do not require chemotherapy among young patients [24]. However, for other molecular subtypes of young breast cancer, we anticipate the development of similar tools in the future.

A higher prevalence of pathogenic variants in cancer susceptibility genes like BRCA1/BRAC2 is observed among young female breast cancer patients when compared to those with late-onset breast cancer [25]. However, due to unavailable data regarding patient's genetic predisposition from the SEER database during grouping and matching processes for this particular study, balancing for potential effects caused by variations within the aforementioned genes could not be achieved. The POSH study analyzed 2733 women and found that patients with pathogenic variants of BRCA1/2 had a comparable prognosis to non-carriers. Patients with BRCA1/2 gene mutations exhibited a 97.0% 2-year overall survival (OS) rate, which was similar to the rate of 96.6% in non-carriers [26]. Another large international multicenter retrospective cohort study involving 1236 breast cancer patients aged ≤ 40 years diagnosed with germline BRCA1/2 mutations demonstrated that BRCA1 carriers had a lower 8-year disease-free survival (DFS) compared to BRCA2 carriers; however, no significant difference was observed in distant recurrence-free interval (DRFI) or overall survival (OS) [27]. Despite the absence of data on BRCA1/2 mutations in this particular study, based on the results from these two

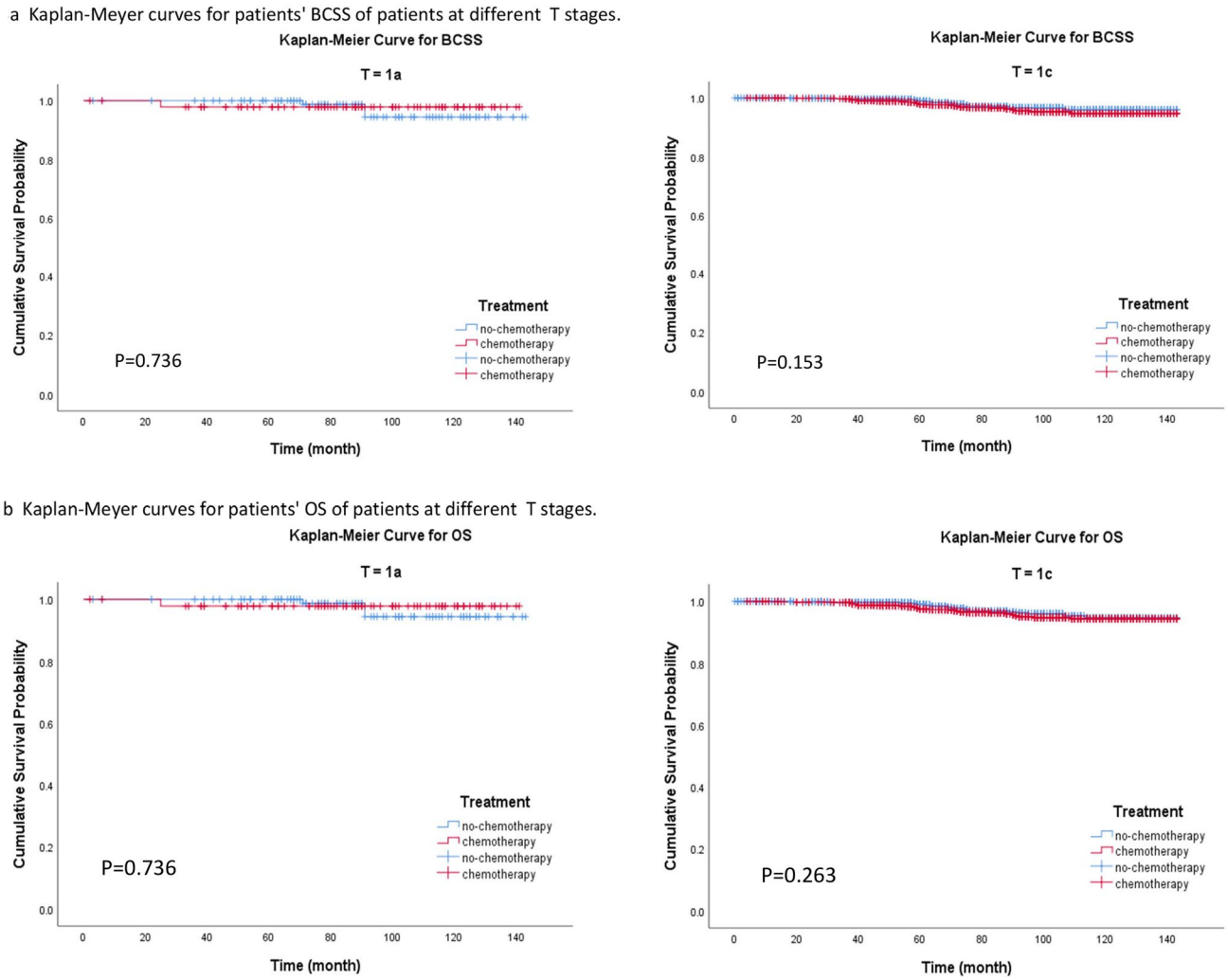

Fig. 3 **a** Kaplan–Meier curves for patients' BCSS of patients at different T stages. **b** Kaplan–Meier curves for patients' OS of patients at different T stages. The log-rank test for *P* are displayed on the graphs

extensive studies, it can be concluded that the mutational status of BRCA1/2 did not impact the study endpoints.

Even more critical than the BRCA gene is the fact that we do not have access to specific regimens for chemotherapy, targeted therapy, and endocrine therapy from the SEER database. Often this information is important for the prognosis of breast cancer patients. Unfortunately, our study population was all premenopausal women in stage Ia and to ensure as much consistency in treatment regimens as possible, we selected patients diagnosed between 2010 and 2020. The consensus of guidelines for young breast cancer during this period shows that chemotherapy during this period is an anthracycline- or zirconia-based regimen; targeted therapy is a 1-year single-targeted treatment with Herceptin; and in terms of endocrine therapy, prolonged therapy and GNRH are still in the research phase, with 5 years of TAM being the choice for most premenopausal women [28]. Admittedly, oncology studies are complex and rigorous, and it is difficult to be exhaustive as the type, number, dose, and cycle of drugs all have an impact on the final outcome. In the randomized controlled study of TAILORx, we were also unable to specify the exact regimen and dosage of chemotherapy and endocrine therapy for all patients [24]. However, as an oncology specialist, we can still get very valuable reference and guidance from it.

We obtained a large, multicenter, and standardized case dataset using the SEER database. By limiting the pathologic type of the tumor to invasive ductal carcinoma, we excluded the effect of different pathologic types on patient prognosis [29]. Efforts were made to reduce the influence of factors such as tumor size, histological grading, molecular typing, and other factors that are now clearly known to affect prognosis on the results of the study through statistical methods such as propensity score matching (PSM). However, it must be acknowledged that retrospective studies still have inherent shortcomings

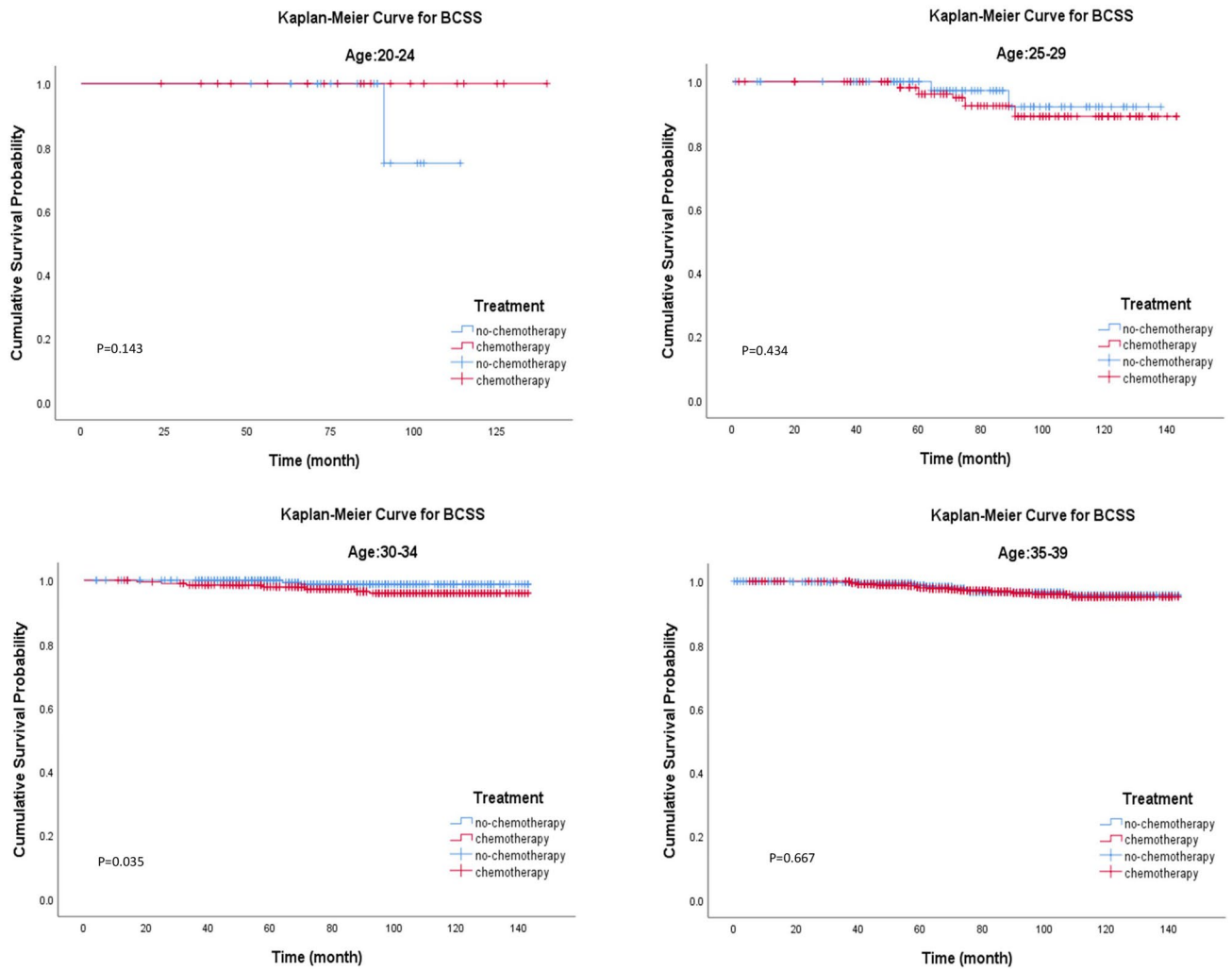

Fig. 4 Kaplan–Meier curves of BCSS in patients of different age groups. The log-rank test for *P* are displayed on the graphs

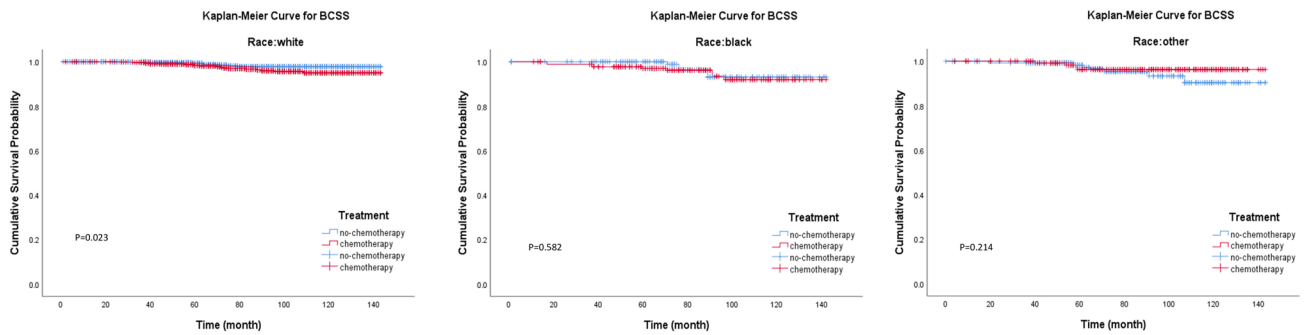

Fig. 5 Kaplan–Meier curves of BCSS in different ethnic groups. The log-rank test for *P* are displayed on the graphs

compared with randomized controlled trials (RCTs), which can introduce unavoidable bias to the study results. The fact that chemotherapy was the standard treatment regimen for the HR-HER2− and HR-HER2+ subgroups resulted in a lower number of pairs in these subgroups after PSM. There were no target events at follow-up, and our study could not perform survival analysis for these subgroups. However, de-escalation therapy for early-stage tumors is the current trend. Chemotherapy was

not found to improve prognosis in stage Ia patients in a retrospective study of 12,156 TNBC patients aged 18–70 years [30]. For early-stage HER2+ breast cancer, the ATTEMPT study still achieved excellent results with the use of novel targeted agents in adjuvant therapy as an alternative to chemotherapy combined with targeted therapy [31]. With the further popularization and improvement of quantitative tests such as Oncotype and Mindact, in the future, the treatment regimen for patients with T1abN0M0 will surely be more accurate, low-toxicity, and efficient.

Conclusion

Based on analysis of real-world clinical data, current evidence suggests that adjuvant chemotherapy does not provide a significant survival benefit for young patients with early-stage breast cancer. Specifically, the potential for therapeutic downstaging exists in a subgroup of young breast cancer patients who are hormone receptor-positive (HR+), lymph node-negative, and have tumors less than 2 cm in size. The integration of advanced gene profiling technologies, particularly multigene expression assays, promises to enable more precise risk stratification and treatment optimization. This paradigm shift toward personalized medicine is expected to improve the quality of life of these patients by significantly reducing chemotherapy-related toxicity while maintaining optimal oncologic outcomes.

Acknowledgements We thank our colleagues in the Department of Breast Surgery, International Peace Maternity and Child Health Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, 200030, China) for their working support. We thank the Breast Department of Ruijin Hospital for allowing us to use the Shanghai Jiao Tong University Breast Cancer Database.

Author contributions SC and WC contributed to the study conception and design. Material preparation, data collection and analysis were performed by SC, XZ, MW, LY and JW. The first draft of the manuscript was written by SC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability The data supporting the results of this study are available from the SEER database and the Shanghai Jiao Tong University Breast Cancer Data Base. We can share these data if the authors request and obtain permission from the SEER database and the Shanghai Jiao Tong University Breast Cancer Data Base.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval All patients in this study were collected from the SEER database and the Shanghai Jiao Tong University Breast Cancer Data Base. And we have got the permission of using the data.

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