Original Article

Evaluation of whether adjuvant chemotherapy can be safely omitted for older female patients with ER-positive, HER2-negative N1 breast cancer: a study based on the SEER database

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Background: This study evaluated the trends and practice patterns associated with adjuvant chemotherapy (CT) use for patients aged ≥70 years with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) N1 (1–3 positive lymph nodes) breast cancer (BC). Furthermore, the relationship between adjuvant CT and survival in this set of patients was determined.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify 6,711 women with ER+, HER2– N1 BC who were aged ≥70 years between 2010 and 2015. Demographic, clinical, and pathological predictors of CT use were identified using logistic regression. Multivariable Cox regression was used to identify variables that correlated with overall survival (OS), before and after propensity score matching (PSM).

Results: Younger age at diagnosis, other histological types, higher tumor grade, larger tumor size, breast reconstruction surgery, progesterone receptor-negative (PR–), and increased nodal involvement were associated with an increased probability of receiving CT. CT use was associated with improved 5-year OS, both before and after PSM [hazard ratio (HR): 0.66, 95% confidence interval (CI): 0.58–0.75 and HR: 0.81, 95% CI: 0.68–0.96, respectively]. The exploratory subgroup analysis showed that although the benefit of CT was significant in the grade III subgroup, it was not significant in the grades I–II subgroups.

Conclusions: Adjuvant CT improved 5-year OS in patients with ER+, HER2– N1 BC who were aged ≥70 years; however, the benefit of CT was more significant in the grade III subgroup than in the grades I–II subgroups.

Keywords: Breast cancer (BC); chemotherapy (CT); older women; survival; treatment de-escalation

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Introduction

Breast cancer (BC) is the most common malignancy among women worldwide, and its incidence increases with age; approximately 50% of BC cases occur in women aged ≥65 years, and >30% occur in women aged ≥70 years (1). With the increase in the life expectancy of people in different populations throughout the world, there will also be an increase in the proportion of BC affecting older women.

Numerous randomized trials and meta-analyses that assessed a large number of published studies have demonstrated the efficacy of adjuvant chemotherapy (CT) for BC (2-6). Women aged ≥70 years are usually excluded from most randomized clinical trials (7), so for

the treatment of older patients with BC, the principles associated with the treatment of their younger counterparts are generally followed.

Retrospective studies have reported a survival benefit following adjuvant CT in older patients with estrogen receptor-negative (ER–) or node-positive BC (8,9). However, a certain proportion of older patients have a short life expectancy and certain comorbidities, which tend to increase the toxic effects of CT and reduce treatment compliance. For older patients with ER-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) N1 (1–3 positive lymph nodes) BC, endocrine therapy (ET), which should be the mainstay of BC treatment, is effective and well tolerated; nevertheless, it is unclear whether older patients with ER+, HER2– N1 BC benefit from undergoing CT in addition to ET.

The aim of this study was to evaluate the trends and practice patterns of adjuvant CT use in patients aged ≥70 years with ER+, HER2– N1 BC. Furthermore, we determined the relationship between adjuvant CT and survival in this set of patients. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3097).

Methods

Study population

We retrospectively reviewed patient data from the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2015. The SEER program, sponsored by the National Cancer Institute, comprises a consortium of 18 regional population-based cancer registries of the USA, covering approximately 30% of the population (10). All female patients aged ≥70 years with ER+ and HER2– BC of stages I–III, T1–T4, and N1, whose data had been included in the SEER database, and who had received postoperative adjuvant ET, were eligible for inclusion in this study. Patients were excluded if they (I) had distant metastasis; (II) did not undergo definitive surgery; (III) had received neoadjuvant CT; (IV) had HER2-positive (HER2+) or triple-negative BC; or (V) had missing data regarding treatment or follow-up. For the included patients, demographic, treatment, pathological, and survival characteristics were obtained, including year of diagnosis; age; race; histological tumor subtype; tumor grade, T stage, and stage according to the system of the American Joint Committee on Cancer (AJCC stage, 7th edition); number of involved nodes; ER status; progesterone receptor (PR) status; HER2 status; type of surgery performed; radiation-treatment status; adjuvant-ET treatment status; adjuvant-CT treatment status; and survival. The present study was based on publicly available data from the database of the SEER program, and we accessed the database with the permission number 26646-Nov2019. This study was approved by the Ethics Committee of The Affiliated Cancer Hospital of Zhengzhou University. Because all patient information in the SEER database is de-identified, informed consent was not required for this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

November 2019 was considered the follow-up cut-off point. For the estimation of overall survival (OS), the time period from the date of initial diagnosis to the date of death from any cause or the follow-up cut-off point was considered.

The demographic, clinical, and pathological characteristics were examined to predict adjuvant CT use in older patients with BC. Continuous variables were evaluated using the *t*-test or Wilcoxon rank-sum test. Categorical variables were evaluated using a chi-squared test or Fisher's exact test. Univariable analyses were performed to identify relevant risk factors ($P<0.05$), which were incorporated into a multivariable stepwise logistic regression model.

Based on whether CT was administered, the patients were divided into an ET group and a CT + ET group. Propensity score matching (PSM) of the ET and CT + ET groups was conducted according to age at diagnosis, year of diagnosis, race, histology, tumor grade, clinical T stage, and AJCC stage, breast surgery strategy, PR status, and regional-node positivity. PSM was conducted using a multivariable logistic regression model. The ET and CT + ET groups were matched at a ratio of 1:1 using a nearest neighbor method (11), with a caliper of 0.05. Univariable and multivariable Cox regression analyses were used to identify variables that correlated with OS, before and after PSM. Kaplan-Meier estimator was used to calculate the 5-year OS of each group, which were then compared using the log-rank test. All statistical analyses were performed using version 3.6.3 of the R software, and differences associated with P values <0.05 were considered statistically significant.

Results

Patient characteristics

Between 2010 and 2015, a total of 6,711 female patients aged ≥70 years with ER+, HER2– N1 BC were enrolled in the SEER database and included in this study. The demographic, clinical, and pathological characteristics of the patients are reported in *Table 1*. Of the 6,711 patients, 1,903 (28.4%) patients received both CT and ET, and 4,808 (71.6%) patients received only ET. There were 2,910 (43.4%) patients aged 70–74 years, 1,970 (29.4%) patients aged 75–79 years, 1,199 (17.9%) patients aged 80–84 years, and 632 (9.4%) patients aged ≥85 years. With respect to the clinical T stage of BC, 3,309 (49.3%) patients had cT1, 2,860 (42.6%) patients had cT2, 407 (6.1%) patients had cT3, and 135 (2.0%) patients had cT4. With respect to the grade of tumor, 1,537 (22.9%) patients had grade I tumors, 3,739 (55.7%) patients had grade II tumors, and 1,435 (21.4%) patients had grade III tumors.

Predictors of CT

The results of adjuvant CT use in older patients are shown in *Table 1*. Adjuvant CT use in older patients declined dramatically with increasing age; 44.5% of those aged 70–74 years, 24.5% of those aged 75–79 years, 8.9% of those aged 80–84 years, and 3.0% of those 85–89 years (P<0.001) received adjuvant CT. The proportion of older patients who received adjuvant CT did not change significantly over time; 28.8% of the patients diagnosed in 2010–2012 and 28.0% of the patients diagnosed in 2013–2015 received adjuvant CT (P=0.512).

The univariable and multivariable logistic regressions of receiving adjuvant CT by individual characteristics are shown in *Table 1*. Younger age at diagnosis (P<0.001), other histological types (P=0.021), higher tumor grade (P<0.001), larger tumor size (P<0.001), breast reconstruction surgery (P=0.002), PR-negative (PR–) (P<0.001), and increased nodal involvement (P<0.001) were all associated with an increased probability of receiving adjuvant CT.

Survival

The demographic and clinical characteristics of older patients with BC before and after PSM are shown in *Table 2*. The median follow-up, calculated using the reverse Kaplan-Meier estimator, was found to be 55 (interquartile range, 38–74) months (12).

The results of the univariable and multivariable Cox regression analyses performed to determine predictive factors of OS, before and after PSM, are shown in *Table 3*. For the entire cohort (n=6,711), before PSM the Cox multivariable analysis revealed several predictors of worse OS, including older age at diagnosis, higher tumor grade, larger tumor size, PR–, increased nodal involvement, omission of radiotherapy, and omission of CT (P<0.05 for each predictor). For the cohort matched exactly (n=3,122) after PSM, another Cox multivariable analysis also revealed several predictors of worse OS, including older age at diagnosis, higher tumor grade, larger tumor size, PR–, increased nodal involvement, omission of radiotherapy, and omission of CT (P<0.05 for each predictor).

In the Kaplan-Meier survival curves, the OS in the CT + ET group was significantly better than that in the ET group, both before and after PSM. Before PSM, the estimated 5-year OS in the CT + ET group was 84.3% and that in the ET group was 77.4% [hazard ratio (HR): 0.66, 95% confidence interval (CI): 0.58–0.75; P<0.001] (*Figure 1A*). After PSM, the estimated 5-year OS in the CT + ET group was 84.2% and that in the ET group was 81.0% (HR: 0.81; 95% CI: 0.68–0.96; P=0.015) (*Figure 1B*).

For the post-PSM population, we conducted an exploratory subgroup analysis and found no significant interactions between the treatment groups and subgroups. The effect of adjuvant CT on OS was consistent across all patient subgroups (*Figure 2*). For patients with grade I and grade II BC, the HRs for the risk of death were 1.23 (95% CI: 0.75–1.99; P=0.41) and 0.80 (95% CI: 0.63–1.01; P=0.06), respectively. For patients with grade III BC, the HR for the risk of death was 0.69 (95% CI: 0.51–0.93; P=0.02) (*Figure 2*).

Discussion

For older patients with ER+, HER2– N1 BC, both undertreatment and overtreatment should be avoided. However, due to the short life expectancy of older patients and the presence of complications, it is difficult to carry out large-scale clinical trials to verify the value of adjuvant CT for this population. Although this was a retrospective study, because of the availability of data for a large number of patients aged ≥70 years with ER+, HER2– N1 BC from the SEER database, we considered that it was possible and important to evaluate the effectiveness of adjuvant CT in this population using this data.

In this study, all included older patients with BC received

Table 1 Univariable and multivariable logistic regression analyses of patient demographic, clinical and pathological characteristics, by CT use

Characteristics	Total (n=6,711)	CT + ET group (n=1,903)	ET group (n=4,808)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
Age at diagnosis, years							
70–74	2,910	1,294 (44.5)	1,616 (55.5)	1.0 (reference)		1.0 (reference)	
75–79	1,970	483 (24.5)	1,487 (75.5)	0.406 (0.357–0.460)	<0.001	0.365 (0.319–0.418)	<0.001
80–84	1,199	107 (8.9)	1,092 (91.1)	0.122 (0.099–0.151)	<0.001	0.095 (0.076–0.118)	<0.001
85+	632	19 (3.0)	613 (97.0)	0.039 (0.024–0.060)	<0.001	0.025 (0.015–0.039)	<0.001
Year of diagnosis							
2010–2012	3,052	878 (28.8)	2,174 (71.2)	1.0 (reference)			
2013–2015	3,659	1,025 (28.0)	2,634 (72.0)	0.964 (0.866–1.072)			
Race							
White	5,692	1,589 (27.9)	4,103 (72.1)	1.0 (reference)			
Black	573	190 (33.2)	383 (66.8)	1.281 (1.065–1.536)	0.008		
Other	446	124 (27.8)	322 (72.2)	0.994 (0.799–1.230)	0.959		
Histology							
Infiltrating duct carcinoma	4,643	1,356 (29.2)	3,287 (70.8)	1.0 (reference)		1.0 (reference)	
Lobular carcinoma	968	276 (28.5)	692 (71.5)	0.967 (0.829–1.126)	0.666	0.889 (0.742–1.064)	0.202
Other	1,100	271 (24.6)	829 (75.4)	0.792 (0.680–0.920)	0.003	0.819 (0.690–0.969)	0.021
Tumor grade							
Well differentiated (I)	1,537	290 (18.9)	1,247 (81.1)	1.0 (reference)		1.0 (reference)	
Moderately differentiated (II)	3,739	1,010 (27.0)	2,729 (73.0)	1.591 (1.376–1.845)	<0.001	1.530 (1.305–1.796)	<0.001
Poorly differentiated (III)	1,435	603 (42.0)	832 (58.0)	3.116 (2.644–3.680)	<0.001	3.118 (2.582–3.771)	<0.001
Clinical T stage							
T1	3,309	750 (22.7)	2,559 (77.3)	1.0 (reference)		1.0 (reference)	
T2	2,860	943 (33.0)	1,917 (67.0)	1.678 (1.500–1.879)	<0.001	1.703 (1.494–1.941)	<0.001
T3	407	161 (39.6)	246 (60.4)	2.233 (1.799–2.765)	<0.001	2.694 (2.070–3.506)	<0.001
T4	135	49 (36.3)	86 (63.7)	1.944 (1.348–2.774)	<0.001	2.387 (1.537–3.688)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=6,711)	CT + ET group (n=1,903)	ET group (n=4,808)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	P value	OR (95% CI)	P value
AJCC stage (7th ed)							
IIA	3,309	750 (22.7)	2,559 (77.3)	1.0 (reference)			
IIB	2,860	943 (33.0)	1,917 (67.0)	1.678 (1.500–1.879)	<0.001		
IIIA	407	161 (39.6)	246 (60.4)	2.233 (1.799–2.765)	<0.001		
IIIB	135	49 (36.3)	86 (63.7)	1.944 (1.348–2.774)	<0.001		
Breast surgery strategy							
Mastectomy	2,989	854 (28.6)	2,135 (71.4)	1.0 (reference)		1.0 (reference)	
BCS	3,449	920 (26.7)	2,529 (73.3)	0.909 (0.815–1.015)	0.089	1.008 (0.885–1.147)	0.909
Reconstruction	273	129 (47.3)	144 (52.7)	2.240 (1.742–2.877)	<0.001	1.544 (1.169–2.038)	0.002
PR status							
Positive	5,899	1,570 (26.6)	4,329 (73.4)	1.0 (reference)		1.0 (reference)	
Negative	812	333 (41.0)	479 (59.0)	1.917 (1.647–2.229)	<0.001	1.925 (1.613–2.298)	<0.001
Regional nodes positive							
1	4,508	1,067 (23.7)	3,441 (76.3)	1.0 (reference)		1.0 (reference)	
2	1,534	548 (35.7)	986 (64.3)	1.792 (1.581–2.031)	<0.001	1.774 (1.541–2.042)	<0.001
3	669	288 (43.0)	381 (57.0)	2.438 (2.060–2.882)	<0.001	2.342 (1.928–2.844)	<0.001
Radiation therapy							
Yes	4,218	1,229 (29.1)	2,989 (70.9)	1.0 (reference)			
No	2,493	674 (27.0)	1,819 (73.0)	0.901 (0.807–1.006)	0.065		

CT, chemotherapy; ET, endocrine therapy; OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; PR, progesterone receptor.

Table 2 Demographic, clinical and pathological characteristics of older BC patients before and after PSM

Characteristics	Before PSM			After PSM		
	CT + ET group (n=1,903)	ET group (n=4,808)	P value	CT + ET group (n=1,561)	ET group (n=1,561)	P value
Age at diagnosis, years			<0.001			0.723
70–74	1,294 (44.5)	1,616 (55.5)		986 (50.7)	960 (49.3)	
75–79	483 (24.5)	1,487 (75.5)		449 (49.4)	460 (50.6)	
80–84	107 (8.9)	1,092 (91.1)		107 (47.1)	120 (52.9)	
85+	19 (3.0)	613 (97.0)		19 (47.5)	21 (52.5)	
Year of diagnosis			0.512			0.251
2010–2012	878 (28.8)	2,174 (71.2)		705 (48.9)	738 (51.1)	
2013–2015	1,025 (28.0)	2,634 (72.0)		856 (51.0)	823 (49.0)	
Race			0.029			0.792
White	1,589 (27.9)	4,103 (72.1)		1,321 (50.2)	1,308 (49.8)	
Black	190 (33.2)	383 (66.8)		143 (49.1)	148 (50.9)	
Other	124 (27.8)	322 (72.2)		97 (48.0)	105 (52.0)	
Histology			0.01			0.702
Infiltrating duct carcinoma	1,356 (29.2)	3,287 (70.8)		1,083 (50.0)	1,083 (50.0)	
Lobular carcinoma	276 (28.5)	692 (71.5)		233 (48.6)	246 (51.4)	
Other	271 (24.6)	829 (75.4)		245 (51.4)	232 (48.6)	
Tumor grade			<0.001			0.801
Well differentiated (I)	290 (18.9)	1,247 (81.1)		280 (50.5)	274 (49.5)	
Moderately differentiated (II)	1,010 (27.0)	2,729 (73.0)		892 (50.3)	882 (49.7)	
Poorly differentiated (III)	603 (42.0)	832 (58.0)		389 (49.0)	405 (51.0)	
Clinical T stage			<0.001			0.311
T1	750 (22.7)	2,559 (77.3)		705 (51.5)	665 (48.5)	
T2	943 (33.0)	1,917 (67.0)		724 (48.6)	765 (51.4)	
T3	161 (39.6)	246 (60.4)		97 (48.3)	104 (51.7)	
T4	49 (36.3)	86 (63.7)		35 (56.5)	27 (43.5)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Before PSM			After PSM		
	CT + ET group (n=1,903)	ET group (n=4,808)	P value	CT + ET group (n=1,561)	ET group (n=1,561)	P value
AJCC stage (7th ed)			<0.001			0.311
IIA	750 (22.7)	2,559 (77.3)		705 (51.5)	665 (48.5)	
IIB	943 (33.0)	1,917 (67.0)		724 (48.6)	765 (51.4)	
IIIA	161 (39.6)	246 (60.4)		97 (48.3)	104 (51.7)	
IIIB	49 (36.3)	86 (63.7)		35 (56.5)	27 (43.5)	
Breast surgery strategy			<0.001			0.405
Mastectomy	854 (28.6)	2,135 (71.4)		663 (48.9)	693 (51.1)	
BCS	920 (26.7)	2,529 (73.3)		816 (51.2)	779 (48.8)	
Reconstruction	129 (47.3)	144 (52.7)		82 (48.0)	89 (52.0)	
PR status			<0.001			0.959
Positive	1,570 (26.6)	4,329 (73.4)		1,343 (50.0)	1,341 (50.0)	
Negative	333 (41.0)	479 (59.0)		218 (50.0)	220 (50.0)	
Regional nodes positive			<0.001			0.955
1	1,067 (23.7)	3,441 (76.3)		950 (50.2)	942 (49.8)	
2	548 (35.7)	986 (64.3)		435 (49.6)	442 (50.4)	
3	288 (43.0)	381 (57.0)		176 (49.9)	177 (50.1)	
Radiation therapy			0.069			
Yes	1,229 (29.1)	2,989 (70.9)				
No	674 (27.0)	1,819 (73.0)				
Vital status			<0.001			
Alive	1,620 (30.0)	3,789 (70.0)				
Dead	283 (21.7)	1,019 (78.3)				

BC, breast cancer; PSM, propensity score matching; CT, chemotherapy; ET, endocrine therapy; OR, odds ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; PR, progesterone receptor.

Table 3 Univariable and multivariable Cox regression analyses for predictive factors of OS before and after PSM

Variables	Before PSM				After PSM			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis, years								
70–74	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
75–79	1.415 (1.219–1.643)	<0.001	1.344 (1.153–1.567)	<0.001	1.668 (1.379–2.019)	<0.001	1.411 (1.160–1.717)	<0.001
80–84	2.395 (2.059–2.786)	<0.001	2.126 (1.807–2.501)	<0.001	2.782 (2.127–3.639)	<0.001	2.283 (1.723–3.025)	<0.001
85+	4.651 (3.978–5.439)	<0.001	3.528 (2.966–4.196)	<0.001	5.683 (3.703–8.724)	<0.001	3.848 (2.482–5.965)	<0.001
Year of diagnosis								
2010–2012	1 (reference)				1 (reference)			
2013–2015	0.976 (0.859–1.109)	0.713			0.934 (0.761–1.147)	0.515		
Race								
White	1 (reference)				1 (reference)		1 (reference)	
Black	1.105 (0.916–1.333)	0.296			1.341 (1.035–1.738)	0.026	1.166 (0.897–1.515)	0.252
Other	0.828 (0.649–1.056)	0.128			0.717 (0.472–1.091)	0.121	0.701 (0.460–1.068)	0.098
Histology								
Infiltrating duct carcinoma	1 (reference)				1 (reference)		1 (reference)	
Lobular carcinoma	1.159 (0.996–1.350)	0.057			1.219 (0.965–1.540)	0.097	0.097	
Other	1.070 (0.923–1.240)	0.37			1.059 (0.832–1.349)	0.641	0.641	
Grade								
Well differentiated (I)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Moderately differentiated (II)	1.216 (1.051–1.405)	0.008	1.094 (0.945–1.267)	0.229	1.367 (1.045–1.788)	0.023	1.193 (0.909–1.564)	0.203
Poorly differentiated (III)	1.671 (1.421–1.965)	<0.001	1.437 (1.215–1.699)	<0.001	1.911 (1.440–2.536)	<0.001	1.464 (1.095–1.956)	0.01
Clinical T stage								
T1	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
T2	1.657 (1.473–1.864)	<0.001	1.389 (1.230–1.569)	<0.001	1.650 (1.361–2.001)	<0.001	1.494 (1.228–1.817)	<0.001
T3	2.088 (1.702–2.563)	<0.001	1.781 (1.445–2.195)	<0.001	2.244 (1.659–3.036)	<0.001	1.836 (1.350–2.497)	<0.001
T4	3.430 (2.589–4.544)	<0.001	2.604 (1.954–3.470)	<0.001	4.299 (2.823–6.545)	<0.001	3.805 (2.475–5.849)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Before PSM				After PSM			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AJCC stage (7th ed)								
IIA	1 (reference)				1 (reference)			
IIB	1.657 (1.473–1.864)	<0.001			1.650 (1.361–2.001)	<0.001		
IIIA	2.088 (1.702–2.563)	<0.001			2.244 (1.659–3.036)	<0.001		
IIIB	3.430 (2.589–4.544)	<0.001			4.299 (2.823–6.545)	<0.001		
Breast surgery strategy								
Mastectomy	1 (reference)				1 (reference)			
BCS	0.624 (0.559–0.698)	<0.001			0.679 (0.569–0.810)	<0.001		
Reconstruction	0.508 (0.357–0.724)	<0.001			0.624 (0.392–0.993)	0.047		
PR status								
Positive	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Negative	1.502 (1.299–1.738)	<0.001	1.366 (1.177–1.585)	<0.001	1.551 (1.251–1.923)	<0.001	1.311 (1.053–1.632)	0.015
Regional nodes positive								
1	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
2	1.062 (0.932–1.211)	0.365	1.014 (0.888–1.157)	0.841	1.071 (0.878–1.308)	0.499	1.040 (0.850–1.272)	0.704
3	1.407 (1.193–1.659)	<0.001	1.237 (1.044–1.466)	0.014	1.524 (1.189–1.954)	<0.001	1.327 (1.029–1.712)	0.029
Systemic therapy								
ET alone	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
CT + ET	0.659 (0.578–0.752)	<0.001	0.824 (0.709–0.958)	0.012	0.808 (0.680–0.960)	0.016	0.831 (0.699–0.988)	0.036
Radiation therapy								
Yes	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	1.852 (1.661–2.064)	<0.001	1.631 (1.460–1.822)	<0.001	1.635 (1.375–1.943)	<0.001	1.658 (1.392–1.976)	<0.001

OS, overall survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; PR, progesterone receptor; CT, chemotherapy; ET, endocrine therapy.

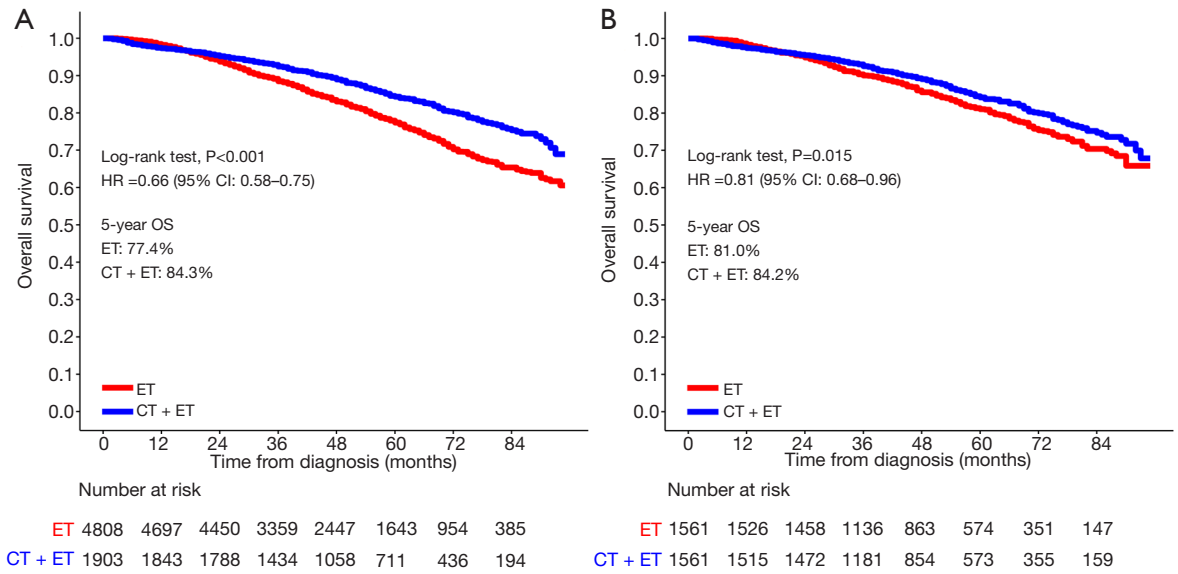

Figure 1 Kaplan-Meier curves comparing OS for the ET versus CT + ET groups in older BC patients. (A) The whole cohort (n=6,711) before PSM. (B) The exact matched cohort (n=3,122) after PSM. OS, overall survival; ET, endocrine therapy; CT, chemotherapy; BC, breast cancer; PSM, propensity score matching.

adjuvant ET; however, the proportion of patients who received adjuvant CT was only 28.4%, which is similar to the proportions reported in previous studies (8,9). We found that although the older patients with ER+, HER2– N1 BC received at least systemic ET, the 5-year OS was only 79.8%. This shows that although the biological behavior of BC in older patients is relatively good, because of certain unique aspects of the older population, some patients cannot receive standard and complete treatment. Further, most older patients have comorbidities, and consequently, with respect to the prognosis of BC, older patients do not have any specific advantage over their younger counterparts. However, in recent years, the life expectancy of older patients with BC has increased significantly. It has been reported that the average remaining life expectancy is almost 16 years for a 70-year-old woman and almost 7 years for an 85-year-old woman (13). Therefore, for older patients with ER+, HER2– N1 BC, the provision of adjuvant CT on the basis of age alone may negatively affect the long-term prognosis of such patients.

In this study, we found that the use of adjuvant CT decreased with increasing age among patients aged ≥70 years with BC, which is consistent with the findings of prior studies (8,14,15). Among older patients, the use of adjuvant CT is limited due to a shorter life expectancy and the prevalence of comorbidities. Studies have found that before the initiation of CT for an older patient with BC, the patient's life expectancy, followed by the benefits and risks of treatment, and finally, the patient's preference must all be accounted for (16,17). We should pay attention to the evidence that among older patients with BC, the number of deaths caused by comorbidities is greater than that caused by the cancer itself (18,19). Meanwhile, caution should be exercised with respect to hospitalizations for adjuvant CT-related adverse events in older patients; in one study, it was found that the hospitalization rate among women aged >64 years who received CT ranged from 13% to 24% (20). Other studies have found that older patients are very hesitant to receive adjuvant CT because they are more concerned about the functional decline and cognitive loss caused by CT than the survival benefits associated with CT (21). This is obviously different from the treatment preference of younger patients, whose primary concern is whether adjuvant CT can cause an improvement in survival. Generally speaking, treatment for older patients should be individualized, and a multidisciplinary team consultation is recommended.

The attributions of cause of deaths in death certificates are known to be error-prone and unreliable, especially for older persons (22,23). Although the SEER database contains information on cause-specific death classifications abstracted from state death certificates, we did not use cancer-specific

Subgroup	All-cause mortality, NO./total NO. CT+ET	ET	Hazard ratio (95% CI)	P value
Age (years)				
70-74	102/978	133/957	0.74(0.57-0.95)	0.02
75-79	85/457	107/469	0.81(0.61-1.08)	0.15
80-84	35/107	34/114	1.19(0.74-1.90)	0.48
≥85	11/19	12/21	1.29(0.56-2.95)	0.55
Year of diagnosis				
2010-2012	161/704	192/734	0.85(0.69-1.05)	0.13
2013-2015	72/857	94/827	0.73(0.53-0.99)	0.04
Race				
White	188/1310	242/1296	0.76(0.63-0.92)	0.00
Black	33/150	33/158	1.09(0.67-1.77)	0.73
Others	12/101	11/107	1.17(0.51-2.65)	0.71
Histology				
Ductal	159/1085	191/1103	0.86(0.70-1.06)	0.15
Lobular	39/232	49/222	0.68(0.45-1.04)	0.08
Others	35/244	46/236	0.72(0.46-1.12)	0.14
Grade				
I	37/280	29/271	1.23(0.75-1.99)	0.41
II	122/880	155/872	0.80(0.63-1.01)	0.06
III	74/401	102/418	0.69(0.51-0.93)	0.02
Clinical T stage				
T1	85/703	84/673	0.98(0.73-1.33)	0.90
T2	114/715	155/747	0.76(0.60-0.97)	0.03
T3	24/109	32/113	0.70(0.41-1.19)	0.19
T4	10/34	15/28	0.54(0.24-1.20)	0.13
AJCC Stage				
IIA	85/703	84/673	0.98(0.73-1.33)	0.90
IIB	114/715	155/747	0.76(0.60-0.97)	0.03
IIIA	24/109	32/113	0.70(0.41-1.19)	0.19
IIIB	10/34	15/28	0.54(0.24-1.20)	0.13
Breast surgery strategies				
Mastectomy	110/675	170/684	0.63(0.50-0.81)	0.00
BCS	112/802	108/800	1.07(0.82-1.39)	0.64
Reconstruction	11/84	8/77	1.04(0.41-2.58)	0.94
Radiation				
Yes	130/1037	152/1029	0.84(0.66-1.06)	0.14
No	103/524	134/532	0.78(0.61-1.01)	0.06
Regional nodes positive				
1	135/967	162/956	0.82(0.65-1.03)	0.09
2	64/428	79/431	0.80(0.58-1.11)	0.19
3	34/166	45/174	0.81(0.52-1.26)	0.34
PR Status				
Positive	190/1334	225/1348	0.86(0.71-1.04)	0.11
Negative	43/227	61/213	0.61(0.42-0.91)	0.01

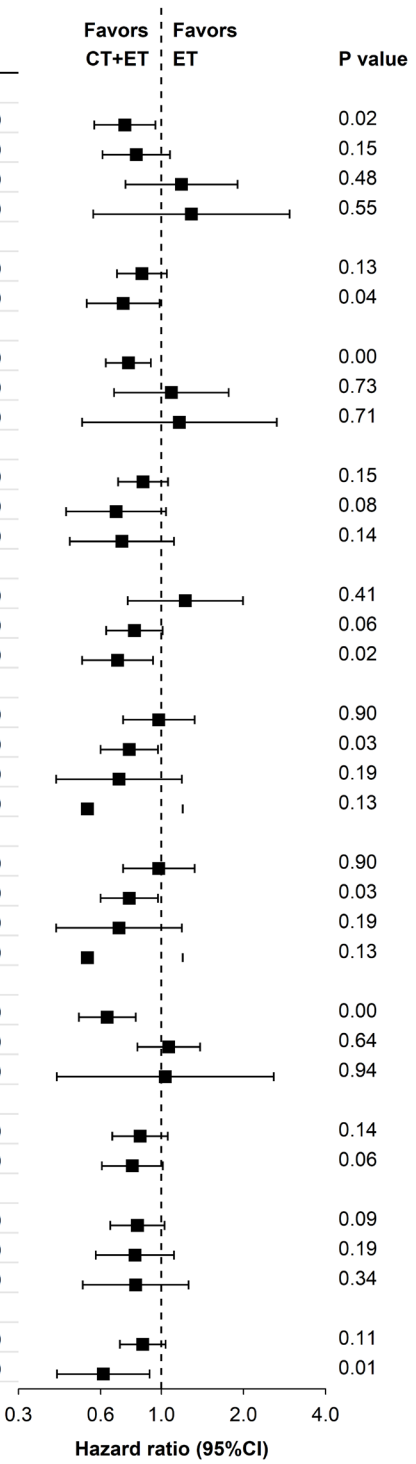

Figure 2 Subgroup analysis of all-cause death in the exact matched cohort (n=3,122) after PSM. PSM, propensity score matching; CT, chemotherapy; ET, endocrine therapy; AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; PR, progesterone receptor.

survival as an endpoint in this study; instead, we used OS as the endpoint. In this study, both before and after PSM, Cox multivariable analyses revealed several predictors of worse OS, including older age at diagnosis, higher tumor grade, larger tumor size, PR–, increased nodal involvement, the omission of radiotherapy, and the omission of CT; these findings are similar to those reported in previous studies (8,9). Meanwhile, both before and after PSM, the Kaplan-Meier survival curves and log-rank test revealed that the 5-year OS in the CT + ET group was significantly better than that in the ET group. Previous meta-analyses have suggested that adjuvant CT is associated with a 13% lower risk of all-cause death in patients with BC who are more than 70 years old (4). Giordano *et al.* also concluded that with respect to patients aged >65 years who had BC of clinical stages I–III, adjuvant CT was associated with a significant reduction in death from BC among patients with ER– and axillary lymph node-positive BC (9). It is well known that in BC management, efforts are continuously made to de-escalate treatment, especially for older patients with ER+, HER2– N1 BC. The prospective RxPONDER trial was designed to evaluate the benefits of CT in patients with ER+, HER2– N1 BC and recurrence score (RS) ≤25, and its results are not expected until 2022 (24). However, in the RxPONDER trial, only 11.6% of patients were older than 70 years, and only patients with RS ≤25 were enrolled. Therefore, even if the results of the RxPONDER trial are published, there will still be a lack of significant prospective research evidence that can be used to clarify the benefits of adjuvant CT in older patients with ER+, HER2– N1 BC. Our study represents one of the largest studies performed to date, in which the utilization of CT for the treatment of patients aged ≥70 years with ER+, HER2– N1 BC and the effect of CT on survival were examined. Based on our findings, we believe that, at present, it may be premature and possibly inappropriate to omit adjuvant CT in this set of patients. The findings of this study may provide clinicians with accurate information that can be used when making decisions regarding the use of adjuvant CT for this population.

The exploratory subgroup analysis showed that while the benefit of adjuvant CT was significant in the subgroup of patients with grade III BC, it was not significant in the grades I–II subgroups. Lee *et al.* concluded that there was a significant correlation between tumor grade and RS; 95% of patients with well-differentiated tumors had low RS, and 56% of patients with poorly/undifferentiated tumors had low RS (25). The interim analysis of the RxPONDER trial, which was presented at the 2020 San Antonio Breast Cancer Symposium, also suggested that adjuvant CT did not benefit postmenopausal patients with ER+, HER2– N1 BC and RS ≤25. Therefore, we speculate that when genetic-testing tools are not available, tumor grade is an important consideration with respect to the use of adjuvant CT for older patients with ER+, HER2– N1 BC.

Several limitations of the current study should be considered. First, investigations of the SEER database are inherently retrospective; consequently, even if statistical methods such as PSM are used, problems such as selection bias cannot be eliminated completely. Second, this study used OS as the endpoint, but OS may be affected by factors unrelated to BC, such as life expectancy and comorbidities. Third, the SEER database does not provide specific information on the CT regimens used, dosages received, number of cycles of administered CT, and complications of CT. Fourth, the SEER database does not have information regarding Ki-67 percentage scores. Fifth, the SEER database does not provide accurate information regarding ET, and we considered the systemic therapy variable as ET. Sixth, the SEER database does not have information regarding duration and adherence to ET.

Conclusions

The use of adjuvant CT decreased with increasing age among patients aged ≥70 years with ER+, HER2– N1 BC. The present results suggest that in this patient population, adjuvant CT improved the 5-year OS in the entire cohort; however, the subgroup analysis suggested that the benefit of CT in grade III subgroup was more significant than that in the subgroups of patients with BC of grades I–II. However, when decisions related to adjuvant CT are made for an older patient with BC, the patient's life expectancy and socioeconomic status, the presence of comorbidities, and the benefits and risks of CT all need to be taken into consideration.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-3097). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of The Affiliated Cancer Hospital of Zhengzhou University. As all patient information in the SEER database is de-identified, informed consent was not necessary. This article does not contain any studies with animals performed by any of the authors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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