The Breast 66 (2022) 24–30

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Treatment and survival outcomes in older women with primary breast cancer: A retrospective propensity score-matched analysis

Yuting Sang [a,b], Benlong Yang [a], Miao Mo [c], Shiyang Liu [a,b], Xujie Zhou [a,b], Jiajian Chen [a], Shuang Hao [a], Xiaoyan Huang [a], Guangyu Liu [a,b], Zhimin Shao [a,b], Jiong Wu [a,b,*]

[a] Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, 200032, China
[b] Department of Oncology, Fudan University Shanghai Medical College, Shanghai, 200032, China
[c] Department of Cancer Prevention, Fudan University Shanghai Cancer Center, Shanghai 200032, China

ARTICLE INFO

Keywords:
Breast cancer
Older women
Treatment strategy
Clinicopathological features
Survival outcomes

ABSTRACT

Purpose: Changes in biological features and functional status make management decisions in older women with primary breast cancer complicated. We aimed to provide an overview of the clinicopathological characteristics and survival outcomes of older breast cancer patients based on the current treatment strategies.

Methods: Female patients diagnosed with primary invasive breast cancer at Fudan University Shanghai Cancer Centre from 2008 to 2016 were included. Patients were divided into a younger group (<65 years) and older group (≥65 years). Propensity score matching was utilised to generate balanced cohorts.

Results: A total of 13,707 patients met the study criteria. Compared with younger patients, older patients had a higher Charlson Comorbidity Index ($p < 0.001$), less lymph node metastasis ($p = 0.009$), more advanced tumour stage ($p = 0.038$), and a larger proportion of estrogen receptor-positive ($p < 0.001$) and epidermal growth factor receptor 2-negative ($p < 0.001$) tumours. Older patients were likely to receive mastectomy and axillary lymph node dissection in addition to a lower proportion of adjuvant chemotherapy. Adjuvant chemotherapy (HR [hazard ratio] 0.69, $p = 0.039$) was independently correlated with better overall survival in the older patients. This survival benefit (HR 0.58, $p = 0.041$) was confirmed in matched cohorts. Among the older patients with larger tumours (HR 0.48, $p = 0.038$) and more lymph node involvement (HR 0.44, $p = 0.040$), adjuvant chemotherapy was associated with a significant survival benefit.

Conclusion: Older breast cancer patients showed less aggressive biological characteristics, intensive surgical and moderate medical preferences. The addition of adjuvant chemotherapy should be considered for older patients, especially for patients with large tumours and more lymph node involvement.

1. Introduction

Female breast cancer has the highest cancer incidence and is the fourth major cause of cancer mortality among women in China [1]. Data indicate that patients aged 60 years or older account for 30% of all breast cancer cases and 46% of all deaths [2]. According to qualified data from the National Central Cancer Registry (NCCR) of China, 31.30% of patients with breast cancer were aged 60 years or older in 2015; by 2030, the proportion of newly diagnosed breast cancer cases in this age group is estimated to be 41.37% [3]. A similar pattern was identified in patients aged ≥65 years [4]. Research reported a shift in the age composition of breast cancer towards older age groups in China, with an increasing median age at diagnosis [5]. Furthermore, the mortality rate was found to increase in older patients according to NCCR data. Compared with younger patients, patients over the age of 60 years have a considerably higher rate of breast cancer mortality, suggesting that older women may obtain little benefit from advances in breast cancer diagnosis and treatment [3]. Therefore, research on different treatment patterns between younger and older patients would help us to identify the factors causing these disparities in mortality and develop strategies to eliminate them. However, most existing studies concentrate on age-specific incidence and mortality in China.

Previous research reported notable differences in tumour pathological features between younger and older individuals with breast cancer. Older patients were found to have a larger proportion of estrogen receptor (ER)- and human epidermal growth factor receptor 2 (HER2)-

* Corresponding author. Department of Breast Surgery, Breast Cancer Institute, Shanghai Cancer Center, Fudan University, Shanghai, 200032, China.
E-mail address: wujiong1122@vip.sina.com (J. Wu).

https://doi.org/10.1016/j.breast.2022.09.001
Received 24 July 2022; Received in revised form 4 September 2022; Accepted 5 September 2022
Available online 6 September 2022
0960-9776/© 2022 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

negative tumours [6–8]. Studies also demonstrated that older patients tended to develop tumours with less aggressive characteristics than their younger counterparts [9–12]. Moreover, studies indicated that comorbidities, toxicity tolerance, functional status, and life expectancy played increasingly essential roles in treatment decisions with ageing [13], which makes decision-making for older patients increasingly complicated [14].

According to treatment guidelines from the National Comprehensive Cancer Network (NCCN), the European Society of Breast Cancer Specialists (EUSOMA), and the International Society of Geriatric Oncology (SIOG), management decisions for breast cancer patients should not depend on their chronological age [15,16]. Instead, therapeutic strategies for older women with breast cancer should consider ageing-related changes in functional status, comorbidities, mental health, and social standing. Geriatric assessment has been recommended as a supplement to oncology assessment for guiding therapeutic interventions in older patients [17,18]. Regarding the detrimental effects on functional status, toxicity, and poor tolerance to chemotherapy, consideration must be given to whether the advantages of surgery and treatment will outweigh the risks for these patients. Based on the available evidence, surgical intervention remains the main option for older individuals and is equally recommended in younger patients. Moreover, a Cochrane review and another retrospective study reported that primary endocrine therapy (PET) had equivalent survival outcomes to surgery in patients aged 70 years and older with ER-positive tumours, while the progression-free survival was worse for PET [19,20]. Recently, a multicentre, prospective study comprising 3416 patients aged ≥70 years further confirmed that surgery was oncologically superior to primary endocrine therapy [21].

Studies have indicated that older patients with comorbidities or poor functional status are less likely to receive chemotherapy [13,22,23]. Moreover, little research has been conducted to investigate the benefits of adjuvant chemotherapy (ACT) in controlled groups of older breast cancer patients, while the available data show inconsistent results. Muss et al. [24] suggested that older women aged 50–69 years with lymph node (LN)-positive breast cancer receiving ACT had a significant reduction in breast cancer mortality and recurrence, while the reduction was progressively diminished with increasing age in patients older than 70 years. Based on the Surveillance, Epidemiology, and End Results (SEER) program dataset, another research demonstrated that ACT was associated with a survival benefit in patients with ER-negative, LN-positive breast cancer, whereas this improvement in survival was not observed among patients with ER-positive disease [25]. Recently, a retrospective study comprising 16,062 patients with triple-negative breast cancer (TNBC) demonstrated that the survival benefit of chemotherapy persisted for LN-negative and LN-positive patients, and even patients with high comorbidity scores [26]. Moreover, study reported survival benefits of ACT in older patients with ER-negative disease, while its detrimental impact on quality of life was resolved after 18 months [27,28]. Given that older women have historically been underrepresented in many breast cancer clinical trials, evidence regarding optimal treatment in older women is scarce, especially for patients in China.

In this study, we compared the differences in clinicopathological characteristics between older (≥65 years) and younger (<65 years) patients and assessed the effectiveness of current therapies on overall survival in older breast cancer patients.

2. Material and methods

2.1. Patients

Female patients diagnosed with primary invasive breast cancer between January 2008 and December 2016 at Fudan University Shanghai Cancer Centre (FUSCC) were enrolled. Patients with bilateral tumours, incomplete comorbidity records, incomplete pathological assessment and follow-up data, those who received neoadjuvant therapy, and those who did not receive any treatment were excluded. A total of 13,707 breast cancer patients met the study criteria and were included in the study (Supplemental Fig. 1). Based on the age at diagnosis, 12,004 patients were assigned to the younger group (<65 years), and 1703 patients were assigned to the older group (≥65 years).

2.2. Data extraction

The patients' demographic, clinicopathological, and treatment data were retrospectively collected by medical record review, which was based on the dataset established by department of cancer prevention in FUSCC. Charlson Comorbidity Index (CCI) score was utilised for quantification of comorbidity, which was calculated based on the severity of the comorbidities documented in the hospital information system [29]. Survival status of patients was extracted from department of clinical statistics of FUSCC based on medical records or telephone follow-up records. Overall survival (OS) was defined as time from primary diagnosis to patient death related to any cause or the last follow-up.

2.3. Clinicopathological characteristics

Given the significant correlation between a CCI score of 3 and therapeutic options and survival outcomes reported in previous studies [30–33], 3 was chosen as the cut-off score for the CCI. CCI scores of 0, 1–2, and ≥3 corresponded to patients with no, few, and major comorbidities, respectively. All pathological variables were determined according to the same guidelines at any time point. Histological subtype was identified using the 2003 and 2012 World Health Organization (WHO) histological classification criteria. The staging of the tumour and axillary LNs were categorized using the 2002 and 2010 American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging criteria. Pathological tumour (pT) and LN (pN) stage was evaluated by pathological assessment after surgery. ER and PR status were identified using immunohistochemistry (IHC). HER2 positivity was defined as IHC 3+ or amplification by fluorescence in situ hybridization (FISH). Accordingly, tumours were divided into four molecular subtypes: (I) luminal A-like (ER- and/or PR-positive, HER2-negative, Ki-67 ≤ 20%); (II) luminal B-like (ER- and/or PR-positive, HER2-negative, Ki-67 > 20%); (III) HER2-positive (HER2-positive and ER- and/or PR-negative, or HER2-positive and ER- and/or PR-positive); and (IV) triple-negative (negative for ER, PR, and HER2).

2.4. Statistical analysis

The Chi-square test was used to compare the clinicopathological data in the younger and older groups. OS was analysed by the Kaplan–Meier method and compared with the log-rank test. Correlated factors of survival were explored with multivariate analysis using Cox proportional hazards. Factors that were considered clinically significant were included in the multivariate model. We used 1:1 propensity score matching (PSM) without replacement to balance the significant variables between groups. For survival analysis between the younger and older groups, matching was based on CCI score, molecular subtype, pT stage, pN stage, type of breast and axillary surgery, and receipt of chemotherapy. For survival analysis between patients with and without ACT, matching was based on age, CCI score, molecular subtype, pT stage, pN stage, and type of breast and axillary surgery. A p-value <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS version 25.0.

3. Results

3.1. Patients

A total of 13,707 patients with invasive breast cancer were involved

in this study. Based on age at diagnosis, 12,004 patients were assigned to the younger group (<65 years) and 1703 patients were assigned to the older group (≥65 years) (Table 1). The data indicated that older women had higher CCI scores ($p < 0.001$), fewer LN metastases ($p = 0.009$), and less advanced tumour stage ($p = 0.038$) than younger women. Invasive ductal carcinoma not otherwise specified (NOS) was the most common histological subtype in both groups, while older patients had a higher percentage of lobular carcinoma NOS and other subtypes ($p < 0.001$). Older patients had a higher proportion of ER-positive ($p < 0.001$) and HER2-negative ($p < 0.001$) tumours. Furthermore, compared with younger patients, luminal A-like and luminal B-like tumours accounted for a substantially higher proportion in older patients ($p < 0.001$). There was no statistically significant difference in tumour size, PR status, or distant metastasis between the two groups.

Table 1
Comparison of clinicopathological characteristics of breast cancer patients between the younger (<65 years) and older groups (≥65 years).

Characteristics	Older group (≥65 years)	Younger group (<65 years)	*P* value
No. of patients	1703	12,004	
Age at diagnosis, median (quartiles, years)	69 (65–92)	49 (18–64)	
CCI score			<0.001
0	995 (58.4)	10,488 (87.4)	
1–2	554 (32.5)	1434 (11.9)	
≥3	154 (0.9)	82 (0.7)	
pT stage			0.111
T0	1 (0.01)	9 (0.1)	
T1	1000 (58.7)	6999 (58.3)	
T2	672 (39.5)	4650 (38.7)	
T3/T4	20 (1.2)	253 (2.1)	
Tx	10 (0.59)	93 (0.8)	
pN stage			0.009
N0	1117 (65.6)	7366 (61.4)	
N1/N2	486 (28.5)	3868 (32.2)	
N3	89 (5.2)	695 (5.8)	
Nx	11 (0.7)	75 (0.6)	
M stage			0.360
M0	1685 (98.9)	11,845 (98.7)	
M1	18 (1.1)	159 (1.3)	
TNM stage			0.038
I	772 (45.3)	5140 (42.8)	
II	694 (40.8)	4882 (40.7)	
III	219 (12.9)	1823 (15.2)	
IV	18 (1.0)	159 (1.3)	
Histological type			<0.001
Invasive duct carcinoma NOS	1296 (76.1)	9016 (75.1)	
Invasive duct carcinoma NOS with DCIS	279 (16.4)	2568 (21.4)	
lobular carcinoma NOS	67 (3.9)	256 (2.1)	
Others	61 (3.6)	164 (1.4)	
ER status			<0.001
Positive	1311 (77.0)	8762 (73.0)	
Negative	392 (23.0)	3242 (27.0)	
PR status			0.504
Positive	1151 (67.6)	7824 (65.2)	
Negative	552 (32.4)	4180 (34.8)	
HER2 status			<0.001
Positive	301 (17.7)	3436 (28.6)	
Negative	1402 (82.3)	8568 (71.4)	
Molecular subtypes			<0.001
Luminal A-like	604 (35.5)	3492 (29.1)	
Luminal B-like	587 (34.5)	3528 (29.4)	
HER2-positive	301 (17.7)	3436 (28.6)	
Triple-negative	211 (12.3)	1548 (12.9)	

Abbreviations: *CCI*, Charlson Comorbidity Index; *pT stage*, pathological tumor stage; *pN stage*, pathological lymph node stage; *M*, distant metastases; *NOS*, not otherwise specified; *DCIS*, ductal carcinoma in situ; *ER*, estrogen receptor; *PR*, progesterone receptor; *HER2*, human epidermal growth factor receptor 2.

3.2. Management patterns

After excluding patients with distant metastases at diagnosis, there were 1685 (98.9%) and 11,845 (98.7%) breast cancer patients initially treated with surgery in the older and younger groups, respectively. Data indicated that elderly patients had a higher rate of mastectomy and lower rate of breast-conserving surgery (BCS) ($p < 0.001$). For axillary evaluation, older patients were inclined to directly undergo axillary lymph node dissection (ALND) or not have axillary surgery ($p < 0.001$). Additionally, most of the younger patients received ACT, whereas more than one-half of the older patients did not receive ACT ($p < 0.001$). Among the patients undergoing ACT, older individuals were less likely to receive regimens containing anthracycline and tended to be administered capecitabine alone (Table 2).

Endocrine therapy was administered to 88.99% (1270/1427) and 88.50% (8531/9639) of the patients with ER- and/or PR-positive tumours in the older and younger groups, respectively. Among the patients with HER2-positive tumours, 44.18% (133/301) of the older patients and 63.65% (2187/3436) of the younger patients received targeted therapy.

3.3. Survival analysis

The median follow-up time was 68.12 months for the entire study cohort. A total of 2088 patients were matched perfectly after PSM between the older and younger patients (Supplemental Table 1). The older patients showed a significantly worse OS compared with younger patients (HR 2.16 [95% CI 1.60–2.92], $p < 0.001$) (Supplemental Fig. 2). Multivariate Cox analysis suggested that the risk of poor OS substantially increased with age. In older patients with a CCI score ≥3, advanced pT and pN stage, luminal B-like, HER2-positive, and TNBC subtype were correlated with poorer OS. ACT was significantly correlated with improved OS. Nevertheless, the type of breast and axillary surgery were not statistically correlated with OS (Table 3).

Table 2
Therapeutic options for breast cancer patients are primarily treated with surgery.

Variables	Older group (N = 1685)	%	Younger group (N = 11,845)	%	*P* value
Breast surgery[a]					<0.001
Breast-conserving surgery	258	15.32	2464	20.80	
Mastectomy	1423	84.45	9095	76.78	
With reconstruction	3	0.18	286	2.42	
Without breast surgery	1[b]	0.06	0	0.00	
Axillary surgery					<0.001
SLNB only	690	40.95	5005	42.25	
SLNB + ALND	145	8.61	1330	11.23	
ALND	825	48.96	5474	46.21	
Without axillary surgery	25	1.48	36	0.30	
Adjuvant chemotherapy					<0.001
With Anthracycline	346	20.53	6645	56.09	
Capecitabine only	72	4.27	7	0.06	
Others	254	15.07	2359	19.92	
Without chemotherapy	902	53.53	2003	16.91	
Missing	111	6.59	831	7.02	

Abbreviations: *SLNB*, sentinel lymph node biopsy; *ALND*, axillary lymph node dissection.

[a] The type of surgery that patients primarily received.

[b] Patient was diagnosed with occult breast cancer and did not receive breast surgery.

Table 3
Multivariable Cox survival analysis in older patients (≥65 years) who received surgery as initial treatment.

Variables	Hazard ratio (95% CI)	*P* value
Age at diagnosis (years)		
65-69 (ref)	–	–
70–74	1.79 (1.29–2.49)	0.001
75–79	1.80 (1.22–2.69)	0.003
80–84	4.36 (2.69–7.08)	<0.001
≥85	6.04 (2.29–15.96)	<0.001
CCI score		
0 (ref)	–	–
1–2	1.10 (0.82–1.48)	0.524
≥3	1.69 (1.15–2.48)	0.007
pT stage		
pT0/pT1 (ref)	–	–
pT2	1.37 (1.03–1.81)	0.027
pT3	2.86 (1.36–5.99)	0.005
pN stage		
pN0 (ref)	–	–
pN1/pN2	2.06 (1.51–2.80)	<0.001
pN3	5.00 (3.18–7.83)	<0.001
Molecular subtypes		
Luminal A-like (ref)	–	–
Luminal B-like	1.47 (1.04–2.08)	0.029
HER2-positive	2.10 (1.40–3.16)	<0.001
Triple-negative	2.35 (1.52–3.64)	<0.001
Breast surgery		
Mastectomy (ref)	–	–
Breast-conserving surgery	1.00 (0.64–1.56)	0.991
Axillary Surgery		
Sentinel lymph node biopsy (ref)	–	–
Axillary lymph node dissection	1.32 (0.95–1.83)	0.098
Without axillary surgery	1.58 (0.65–3.84)	0.312
Adjuvant chemotherapy		
No (ref)	–	–
Yes	0.69 (0.49–0.98)	0.039

Abbreviations: *ref*, reference; *95% CI*, 95% confidence interval; *CCI*, Charlson Comorbidity Index; *pT stage*, pathological tumor stage; *pN stage*, pathological lymph node stage; *HER2*, human epidermal growth factor receptor 2.

3.4. Survival analysis after propensity score matching

We further verified the effect of ACT in a matched cohort. After PSM, 224 patients with ACT and 224 patients without ACT were matched successfully (Table 4). Patients receiving ACT showed improved OS compared with those who did not receive ACT (HR 0.58 [95% CI 0.35–0.96], p = 0.041) (Fig. 1). Subgroup analysis suggested that chemotherapy was favourable in patients with larger tumour size (HR 0.48 [95% CI 0.24–0.96], p = 0.038) and more LN involvement (HR 0.40 [95% CI 0.20–0.96], p = 0.040) (Fig. 2). However, no significant improvement in survival was observed in patients from different age groups, CCI scores, and molecular subtypes.

4. Discussion

In the present study, we demonstrated significant differences in clinicopathological characteristics and treatment patterns between older women and their younger counterparts with primary invasive breast cancer. Our data suggested that ACT was independently correlated with an apparent survival benefit in patients aged ≥65 years.

Retrospective studies reported that ageing not only increased the incidence of comorbidities but also influenced the clinicopathological features of breast cancer patients [6–8,11]. Our result indicated that older patients tended to be diagnosed with less aggressive tumours at a less advanced stage, which included a higher proportion of ER-positive, HER2-negative tumours and less LN involvement. Although previous studies suggested that older women were more likely to have large tumours [34–36], no significant difference in tumour size was identified between the two groups in our study. A possible explanation might be the development and promotion of breast cancer screening in recent decades. The most common histological subtype of invasive breast cancer in our cohort was ductal carcinoma. Moreover, we identified a lower percentage of ductal carcinoma and higher percentage of lobular carcinoma, a special type of invasive breast cancer. Similar trends in the incidence of different histological types were reported by Albrektsen

Table 4
Balanced statistics of patients aged over 65 years with or without adjuvant chemotherapy (ACT) after propensity score matching.

Variables	Pre-matching			Post-matching		
	With ACT (N = 672)	Without ACT (N = 902)	*P* value	With ACT (N = 224)	Without ACT (N = 224)	*P* value
Age at diagnosis (years)			<0.001			1.000
65-69 (ref)	496 (73.8)	379 (42.0)		154 (68.8)	154 (68.8)	
70–74	130 (19.3)	269 (29.8)		52 (23.2)	52 (23.2)	
75–79	37 (5.5)	180 (20.0)		15 (6.7)	15 (6.7)	
80–84	9 (1.3)	65 (7.2)		3 (1.3)	3 (1.3)	
≥85	0 (0.0)	9 (0.1)		–	–	1.000
CCI score			0.863			
0	396 (58.9)	526 (58.3)		144 (64.3)	144 (64.3)	
1–2	218 (32.5)	291 (32.3)		62 (27.7)	62 (27.7)	
≥3	58 (8.6)	85 (9.4)		18 (8.0)	18 (8.0)	
pT stage			<0.001			1.000
T1	327 (48.7)	606 (67.2)		135 (60.3)	135 (60.3)	
T2	332 (49.4)	282 (31.3)		87 (38.8)	87 (38.8)	
T3	13 (1.9)	14 (1.6)		2 (0.9)	2 (0.9)	
pN stage			<0.001			1.000
pN0	314 (46.7)	734 (81.4)		165 (73.7)	165 (73.7)	
pN1/pN2	290 (43.2)	156 (17.3)		57 (25.4)	57 (25.4)	
pN3	68 (10.1)	12 (1.3)		2 (0.9)	2 (0.9)	
Molecular subtypes			0.478			1.000
Luminal A-like	229 (34.1)	337 (37.4)		71 (31.7)	71 (31.7)	
Luminal B-like	237 (35.3)	308 (34.1)		98 (43.8)	98 (43.8)	
HER2-positive	125 (18.6)	147 (16.3)		33 (14.7)	33 (14.7)	
Triple-negative	81 (12.1)	110 (12.2)		22 (9.8)	22 (9.8)	
Breast surgery			<0.001			1.000
Breast-conserving surgery	68 (10.1)	176 (19.5)		24 (10.7)	24 (10.7)	
Mastectomy	604 (89.9)	726 (80.5)		200 (89.3)	200 (89.3)	
Axillary surgery			<0.001			1.000
SLNB	183 (27.2)	463 (51.3)		112 (50.0)	112 (50.0)	
ALND	487 (72.5)	419 (46.5)		112 (50.0)	112 (50.0)	
Without axillary surgery	2 (0.3)	20 (2.2)		–	–	

Abbreviations: *CCI*, Charlson Comorbidity Index; *ACT*, adjuvant chemotherapy; *pT stage*, pathological tumor stage; *pN stage*, pathological lymph node stage; *HER2*, human epidermal growth factor receptor 2; *SLNB*, sentinel lymph node biopsy; *ALND*, axillary lymph node dissection.

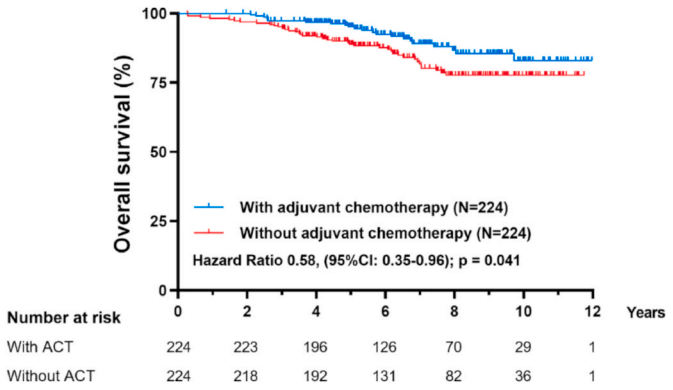

Fig. 1. Kaplan-Meier plots for overall survival in the matched cohort of patients with (N = 224) and without (N = 224) adjuvant chemotherapy.

et al. [37] and Fisher et al. [38].

Despite the recent application of new surgical techniques, including BCS, sentinel LN biopsy, and breast reconstruction, we reported higher rates of mastectomy in patients older than 65 years compared with studies from developed areas [39–43]. This status of therapeutic options was consistent with recent research based on 110 hospitals in China [44]. One possible explanation might be that older patients were more conservative due to extensive tension and anxiety about cancer, which was attributed to their poor functional status and comorbidities [45,46]. In addition, older patients focused less attention on cosmic outcomes and were more inclined to undergo mastectomy to avoid radiotherapy after BCS [44]. However, surgery remains the standard treatment option in older patients with operable breast cancer [15,22] and was reported to be correlated with a survival benefit in patients older than 80 years [47,48]. Considering the passive clinicopathological features, surgical trends in the elderly are quite aggressive in China. According to the results of the NASBP B-06, BCS plus radiotherapy was considered an alternative to mastectomy [49]. Furthermore, based on SEER data, no differences in survival between older breast cancer patients who underwent mastectomy and BCS were identified in the functional status-controlled groups [50]. Similarly, our data indicated that surgical type did not influence survival outcomes in older patients. Overall, the surgical practices of the breast in China were quite different from those in developed countries, which indicated that implementation of consensus and guidelines for breast cancer needs further promotion in addition to a potential insufficiency in evidence-based decision-making in elderly individuals.

ALND was more prevalent in older patients than younger patients, even in cases with less LN metastasis. However, omission of axillary surgery or substitution by other adjuvant therapy options in certain groups of elderly patients has been proven to be safe. IBCSG 10–93, a randomised-controlled trial, identified no improvement in disease-free survival or OS in patients aged ≥60 years with clinically node-negative operable breast cancer after addition of ALND [51]. Similarly, an Italian study indicated no survival benefit from ALND in women aged 65–80 years after 15 years of follow-up [52]. Consistently, we found that type of axillary surgery was not associated with significantly better OS. Given that SLNB was effective in pathologic nodal staging and cancer control and was associated with a significant decline in arm morbidity [53–55], it is a rational alternative to ALND in elderly patients. Altogether, our results suggest a conservative attitude of older patients towards SLNB and insufficient consultation of current evidence by surgeons and patients during the treatment decision-making process in older patients in current clinical practice.

ACT was independently correlated with a decreased risk of mortality in elderly breast cancer patients. However, our data reported a lower proportion of ACT among older patients, which was consistent with earlier studies [25,56–59]. One possible explanation might be that the comorbidities, geriatric syndromes, frailty, and limited life expectancy become more serious with ageing, which leads to progressively poorer acceptance of standard chemotherapy. However, based on the balanced cohorts in the current study, ACT was found to be associated with better OS. Subgroup analysis further indicated that patients with large tumour size and more LN involvement could benefit from ACT. In addition, an increased incidence of single capecitabine application was identified in elderly patients. According to the results of the CALGB 49907 study, standard chemotherapy is superior to capecitabine monotherapy in terms of relapse-free survival and OS, especially in older patients with hormone receptor-negative disease [23,60]. Moreover, compared with

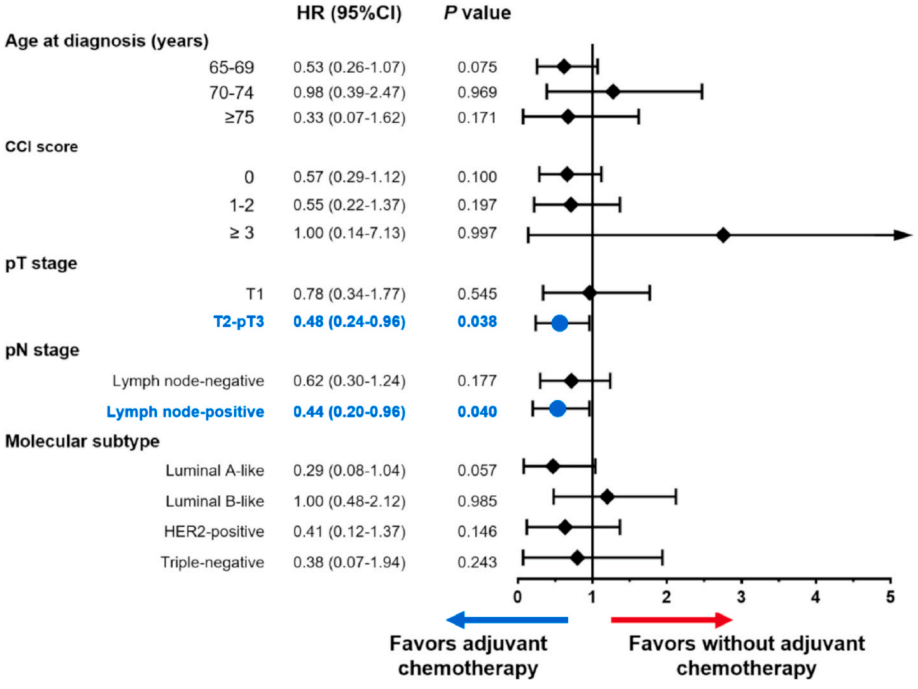

Fig. 2. Subgroup analysis of impact factors in propensity score-matched cohort (N = 448).

standard chemotherapy, the advantage of capecitabine on quality of life during treatment was found to be equivalent at 1 year [61].

The major limitation of the present study was caused by the nature of retrospective studies, which made selection bias inevitable regarding patients' options for postoperative treatment. As the cancer centre with more than 2000 breast cancer patients diagnosed and hospitalised every year since 2010, a large proportion of elderly patients are from other cities in China [5,62]. However, due to a lack of convenience and socioeconomic problems, elderly patients are inclined to return to the local area for subsequent adjuvant treatment and regular follow-up. In addition, based on the experience of surgeons at the clinic, older patients had a relatively passive attitude towards standard treatment. Therefore, a higher percentage of missing records on complete pathological assessment, complete follow-up data, and therapeutic information were identified in older patients. Therefore, the cohort of the current study may not be sufficient to reflect the pathological and therapeutic features of all elderly Chinese patients with breast cancer. Moreover, a large proportion of older patients were excluded from our analysis because they were diagnosed with ductal carcinoma in situ, which lead to an even lower proportion of patients aged ≥65 years in the current study. Without the specific cause of death, we can only analyse OS instead of breast cancer-specific survival, which would provide better assessment of therapeutic benefits in elderly patients. Regarding postoperative therapy, the completion status of endocrine and targeted therapy was absent in many patients, and intermittent adherence or discontinuance of the regimens led to inadequate data for survival analysis among patients with or without endocrine and targeted therapy. Moreover, due to the lack of geriatric assessment, we utilised age and CCI score to broadly assess the functional status of patients based on the retrospectively collected data regarding comorbidities. Previous studies reported that age was significantly correlated with poorer survival outcomes, and optimal therapeutic strategies varied based on the age of elderly patients [36,63]. Therefore, age-stratified studies concentrating on the treatment of elderly patients should be conducted in China. All the limitations of the present study should be taken into consideration, and randomised-control studies are needed to further confirm our findings.

5. Conclusions

We provided a brief overview of the distinct clinicopathological features, more aggressive surgical choices, and moderate chemotherapy preferences of breast cancer patients aged ≥65 years compared with their younger counterparts. Our results support the administration of ACT, especially in older patients with large tumour size and LN involvement.

Funding

This study was supported in part by grants from the National Key R&D Program of China (2017YFC1311004).

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethics approval

The study was conducted following the Declaration of Helsinki (as revised in 2013). This research has been approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Centre. Informed consent has been waived by the ethics committee as this retrospective research poses no risk to patients.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yuting Sang. The first draft of the manuscript was written by Yuting Sang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

None.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.09.001.

References

[1] Cao W, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J (Engl). 2021;134:783–91.
[2] Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
[3] Lei S, Zheng R, Zhang S, Chen R, Wang S, Sun K, et al. Breast cancer incidence and mortality in women in China: temporal trends and projections to 2030. Cancer Biol Med; 2021.
[4] Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. Breast cancer in China. Lancet Oncol 2014;15:e279–89.
[5] Fan L, Zheng Y, Yu KD, Liu GY, Wu J, Lu JS, et al. Breast cancer in a transitional society over 18 years: trends and present status in Shanghai, China. Breast Cancer Res Treat 2009;117:409–16.
[6] Rhodes A, Jasani B, Balaton AJ, Barnes DM, Miller KD. Frequency of oestrogen and progesterone receptor positivity by immunohistochemical analysis in 7016 breast carcinomas: correlation with patient age, assay sensitivity, threshold value, and mammographic screening. J Clin Pathol 2000;53:688–96.
[7] Cheung KL, Wong AW, Parker H, Li VW, Winterbottom L, Morgan DA, et al. Pathological features of primary breast cancer in the elderly based on needle core biopsies–a large series from a single centre. Crit Rev Oncol Hematol 2008;67:263–7.
[8] Syed BM, Green AR, Ellis IO, Cheung KL. Human epidermal growth receptor-2 overexpressing early operable primary breast cancers in older (>/=70 years) women: biology and clinical outcome in comparison with younger (<70 years) patients. Ann Oncol 2014;25:837–42.
[9] Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 2000;92:550–6.
[10] Eppenberger-Castori S, Moore Jr DH, Thor AD, Edgerton SM, Kueng W, Eppenberger U, et al. Age-associated biomarker profiles of human breast cancer. Int J Biochem Cell Biol 2002;34:1318–30.
[11] Syed BM, Green AR, Paish EC, Soria D, Garibaldi J, Morgan L, et al. Biology of primary breast cancer in older women treated by surgery: with correlation with long-term clinical outcome and comparison with their younger counterparts. Br J Cancer 2013;108:1042–51.
[12] Mathew J, Lee S, Syed BM, Morgan DA, Ellis IO, Cheung KL. A study of ductal versus non-ductal invasive breast carcinomas in older women: long-term clinical outcome and comparison with their younger counterparts. Breast Cancer Res Treat 2014;147:671–4.
[13] Giordano SH, Hortobagyi GN, Kau SW, Theriault RL, Bondy ML. Breast cancer treatment guidelines in older women. J Clin Oncol 2005;23:783–91.
[14] Battisti NML, Joshi K, Nasser MS, Ring A. Systemic therapy for older patients with early breast cancer. Cancer Treat Rev 2021;100:102292.
[15] National Comprehensive Cancer Network. (NCCN) clinical practice guidelines in oncology. Older Adult oncology, Version 1. 2021. . 2021.
[16] Biganzoli L, Battisti NML, Wildiers H, McCartney A, Colloca G, Kunkler IH, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol 2021;22:e327–40.
[17] Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018;36:2326–47.
[18] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595–603.
[19] Syed BM, Al-Khyatt W, Johnston SJ, Wong DW, Winterbottom L, Kennedy H, et al. Long-term clinical outcome of oestrogen receptor-positive operable primary breast cancer in older women: a large series from a single centre. Br J Cancer 2011;104:1393–400.

[20] Hind D, Wyld L, Beverley CB, Reed MW. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev 2006:CD004272.
[21] Wyld L, Reed MWR, Morgan J, Collins K, Ward S, Holmes GR, et al. Bridging the age gap in breast cancer. Impacts of omission of breast cancer surgery in older women with oestrogen receptor positive early breast cancer. A risk stratified analysis of survival outcomes and quality of life. Eur J Cancer 2021;142:48–62.
[22] Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, et al. Management of elderly patients with breast cancer: updated recommendations of the international society of geriatric oncology (SIOG) and European society of breast cancer Specialists (EUSOMA). Lancet Oncol 2012;13:e148–60.
[23] Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055–65.
[24] Muss HB, Woolf S, Berry D, Cirrincione C, Weiss RB, Budman D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. JAMA 2005;293:1073–81.
[25] Giordano SH, Duan Z, Kuo YF, Hortobagyi GN, Goodwin JS. Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J Clin Oncol 2006;24:2750–6.
[26] Crozier JA, Pezzi TA, Hodge C, Janeva S, Lesnikoski BA, Samiian L, et al. Addition of chemotherapy to local therapy in women aged 70 years or older with triple-negative breast cancer: a propensity-matched analysis. Lancet Oncol 2020;21:1611–9.
[27] Ring A, Battisti NML, Reed MWR, Herbert E, Morgan JL, Bradburn M, et al. Bridging the Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer. Br J Cancer 2021;125:209–19.
[28] Battisti NML, Reed MWR, Herbert E, Morgan JL, Collins KA, Ward SE, et al. Bridging the Age Gap in breast cancer: impact of chemotherapy on quality of life in older women with early breast cancer. Eur J Cancer 2021;144:269–80.
[29] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–51.
[30] Viuff JH, Vejborg I, Schwartz W, Bak M, Mikkelsen EM. Morbidity as a predictor for participation in the Danish national mammography screening program: a cross-sectional study. Clin Epidemiol 2020;12:509–18.
[31] Morgan JL, Richards P, Zaman O, Ward S, Collins K, Robinson T, et al. The decision-making process for senior cancer patients: treatment allocation of older women with operable breast cancer in the UK. Cancer Biol Med 2015;12:308–15.
[32] Ording AG, Cronin-Fenton DP, Jacobsen JB, Norgaard M, Thomsen RW, Christiansen P, et al. Comorbidity and survival of Danish breast cancer patients from 2000-2011: a population-based cohort study. Clin Epidemiol 2013;5:39–46.
[33] Land LH, Dalton SO, Jensen MB, Ewertz M. Impact of comorbidity on mortality: a cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990-2008. Breast Cancer Res Treat 2012;131:1013–20.
[34] Eaker S, Dickman PW, Bergkvist L, Holmberg L. Uppsala/Orebro Breast Cancer G. Differences in management of older women influence breast cancer survival: results from a population-based database in Sweden. PLoS Med 2006;3:e25.
[35] Wallwiener CW, Hartkopf AD, Grabe E, Wallwiener M, Taran FA, Fehm T, et al. Adjuvant chemotherapy in elderly patients with primary breast cancer: are women >/=65 undertreated? J Cancer Res Clin Oncol 2016;142:1847–53.
[36] Schonberg MA, Marcantonio ER, Li D, Silliman RA, Ngo L, McCarthy EP. Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol 2010;28:2038–45.
[37] Albrektsen G, Heuch I, Thoresen SO. Histological type and grade of breast cancer tumors by parity, age at birth, and time since birth: a register-based study in Norway. BMC Cancer 2010;10:226.
[38] Fisher CJ, Egan MK, Smith P, Wicks K, Millis RR, Fentiman IS. Histopathology of breast cancer in relation to age. Br J Cancer 1997;75:593–6.
[39] Besic N, Besic H, Peric B, Pilko G, Petric R, Zmuc J, et al. Surgical treatment of breast cancer in patients aged 80 years or older–how much is enough? BMC Cancer 2014;14:700.
[40] Bouchardy C, Rapiti E, Fioretta G, Laissue P, Neyroud-Caspar I, Schafer P, et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003;21:3580–7.
[41] Grumpelt AM, Ignatov A, Tchaikovski SN, Burger E, Costa SD, Eggemann H. Tumor characteristics and therapy of elderly patients with breast cancer. J Cancer Res Clin Oncol 2016;142:1109–16.
[42] Jonczyk MM, Jean J, Graham R, Chatterjee A. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. Breast Cancer Res Treat 2019;173:267–74.
[43] Clough KB, Acosta-Marin V, Nos C, Alran S, Rouanet P, Garbay JR, et al. Rates of neoadjuvant chemotherapy and oncoplastic surgery for breast cancer surgery: a French national survey. Ann Surg Oncol 2015;22:3504–11.
[44] Yang B, Ren G, Song E, Pan D, Zhang J, Wang Y, et al. Current status and factors influencing surgical options for breast cancer in China: a nationwide cross-sectional survey of 110 hospitals. Oncol 2020;25:e1473–80.
[45] Field TS, Bosco JL, Prout MN, Gold HT, Cutrona S, Pawloski PA, et al. Age, comorbidity, and breast cancer severity: impact on receipt of definitive local therapy and rate of recurrence among older women with early-stage breast cancer. J Am Coll Surg 2011;213:757–65.
[46] Fisher CS, Martin-Dunlap T, Ruppel MB, Gao F, Atkins J, Margenthaler JA. Fear of recurrence and perceived survival benefit are primary motivators for choosing mastectomy over breast-conservation therapy regardless of age. Ann Surg Oncol 2012;19:3246–50.
[47] Ojala K, Meretoja TJ, Mattson J, Leidenius MHK. Surgical treatment and prognosis of breast cancer in elderly - a population-based study. Eur J Surg Oncol 2019;45:956–62.
[48] de Boer AZ, de Glas NA, Marang-van de Mheen PJ, Dekkers OM, Siesling S, de Munck L, et al. Effect of omission of surgery on survival in patients aged 80 years and older with early-stage hormone receptor-positive breast cancer. Br J Surg 2020;107:1145–53.
[49] Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[50] Mogal HD, Clark C, Dodson R, Fino NF, Howard-McNatt M. Outcomes after mastectomy and lumpectomy in elderly patients with early-stage breast cancer. Ann Surg Oncol 2017;24:100–7.
[51] International Breast Cancer Study G, Rudenstam CM, Zahrieh D, Forbes JF, Crivellari D, Holmberg SB, et al. Randomized trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of International Breast Cancer Study Group Trial 10-93. J Clin Oncol 2006;24:337–44.
[52] Martelli G, Boracchi P, Orenti A, Lozza L, Maugeri I, Vetrella G, et al. Axillary dissection versus no axillary dissection in older T1N0 breast cancer patients: 15-year results of trial and out-trial patients. Eur J Surg Oncol 2014;40:805–12.
[53] Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American college of surgeons oncology group (alliance) ACOSOG Z0011 randomized trial. Ann Surg 2016;264:413–20.
[54] Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303–10.
[55] Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. Cancer 2000;88:608–14.
[56] Brunello A, Basso U, Pogliani C, Jirillo A, Ghiotto C, Koussis H, et al. Adjuvant chemotherapy for elderly patients (> or =70 years) with early high-risk breast cancer: a retrospective analysis of 260 patients. Ann Oncol 2005;16:1276–82.
[57] Hawfield A, Lovato J, Covington D, Kimmick G. Retrospective study of the effect of comorbidity on use of adjuvant chemotherapy in older women with breast cancer in a tertiary care setting. Crit Rev Oncol Hematol 2006;59:250–5.
[58] Peters E, Anzeneder T, Jackisch C, Dimpfl T, Kunz G, Katalinic A, et al. The treatment of primary breast cancer in older women with adjuvant therapy: a retrospective analysis of data from over 3000 patients from the path biobank, with two-year follow-up. Dtsch Arztebl Int 2015;112:577–84.
[59] Delgado-Ramos GM, Nasir SS, Wang J, Schwartzberg LS. Real-world evaluation of effectiveness and tolerance of chemotherapy for early-stage breast cancer in older women. Breast Cancer Res Treat 2020;182:247–58.
[60] Muss HB, Polley MC, Berry DA, Liu H, Cirrincione CT, Theodoulou M, et al. Randomized trial of standard adjuvant chemotherapy regimens versus capecitabine in older women with early breast cancer: 10-year update of the CALGB 49907 trial. J Clin Oncol 2019;37:2338–48.
[61] Kornblith AB, Lan L, Archer L, Partridge A, Kimmick G, Hudis C, et al. Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. J Clin Oncol 2011;29:1022–8.
[62] Jia-Jian C, Nai-Si H, Jing-Yan X, Ben-Long Y, Guang-Yu L, Gen-Hong D, et al. Current status of breast reconstruction in southern China: a 15 Year, single institutional experience of 20,551 breast cancer patients. Medicine (Baltim) 2015;94:e1399.
[63] Bastiaannet E, Liefers GJ, de Craen AJ, Kuppen PJ, van de Water W, Portielje JE, et al. Breast cancer in elderly compared to younger patients in The Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat 2010;124:801–7.