Clinicopathological features and treatment sensitivity of elderly Chinese breast cancer patients

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Abstract. This study aimed to determine the clinicopathological features and treatment sensitivity of elderly breast cancer patients in China. The clinical data of 594 elderly breast cancer patients of 70 or more years of age were collected and compared to those of 657 patients of less than 70 years of age to analyze whether breast cancer in the elderly is different and whether the difference affected outcome. The median age was 75.2 years in the elderly patients and 49.8 years in the young patients. Age of menarche, parous status and body mass index were similar in the two groups. A higher frequency of steroid receptor-positive rate, a lower expression of HER-2 and p53, less axillary node-positive rate and earlier tumor stage were found in patients of 70 years or older. The 5-year relapse-free survival (RFS) and overall survival (OS) was 77 and 82% in the elderly and 86 and 93% in the young patients, respectively. Patients with estrogen receptor (ER)-positive or lymph node (LN)-negative cancers showed a more favorable outcome in the elderly patients. RFS and OS were increased in elderly patients who underwent endocrine therapy or omitted chemotherapy. Breast cancer in the elderly had more favorable tumor features, using estrogen receptor and lymph node status as prognostic factors. It was therefore concluded that adjuvant endocrine therapy may benefit elderly patients, while chemotherapy may not.

Introduction

Breast cancer is the most commonly diagnosed cancer in women all over the world and the leading cause of cancer-related death (1). Age is the greatest risk factor for the development of new cases of breast cancer, and the incidence increases with age: 1 in 50 by age 50, 1 in 14 by age 70 and 1 in 9 by age 85 (2). Approximately 50% of breast cancers occur in women of 65 years of age or older and 35% occur after the age of 70 (3). Breast cancer has benefitted from mortality-lowering earlier diagnosis and more effective treatments in the last three decades, but studies regarding possible differences in the biology and clinical outcomes of breast cancer according to age are relatively limited, owing to the fact that elderly women have been excluded from large randomized controlled trials (4,5).

In spite of the paucity of data, physicians consider age to be an important determinant of therapy. Median life expectancy is calculated to be 14.8 years for women of 70 years, while at 80 years the median survival remains 8.4 years, even though it is often underestimated by clinicians (6). However, co-morbid diseases affect choice of treatment, with a 20-fold higher rate of non-breast cancer mortality in patients with three or more significant co-morbidities (7). Therefore, mobility, cognition, concurrent medications and social factors should be taken into consideration when determining the proper treatment for older patients (8).

The tumor features and outcome of elderly breast cancer in the Chinese population have yet to be reported. Furthermore, the sensitivity of systemic adjuvant therapies in elderly patients has yet to be reported in this population. Taking these factors into account, a retrospective analysis was performed in order to better understand the nature of elderly breast cancer and determine the prognostic factors and treatment sensitivity of elderly patients.

Materials and methods

Patients. This study was based on the retrospective analysis of our department's database. The selection criteria of the case group were: female gender, ≥70 years of age, with pathologically diagnosed breast cancer and surgery at our institute. A total of 594 patients meeting the selection criteria and treated from August 1991 to October 2006 were identified in this database. A control group of 657 patients aged <70 years was selected and randomized from the same database by age and year of diagnosis. Data recorded on the database for each patient included age at diagnosis, date of diagnosis, menarche age, body mass index (BMI), marriage status, family history of cancer, diagnostic method, clinical stage, treatment details (surgery and adjuvant therapy),

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histopathological features [tumor size, lymph node (LN) status, estrogen/progesterone receptor (ER/PR) and Her-2 expression] and follow-up information. Routine follow-up was carried out every 3 months after diagnosis during the first 2 years, every 6 months during the following 2 years and then once annually. Follow-up information was obtained from hospital and office records and from the patients and their families. The date of the last follow-up and date of recurrence or death were recorded.

The stage was determined from pathological records and classified according to the AJCC TNM guidelines. We defined stages 0, I and II as 'early stage' and stages III and IV as 'advanced stage'. Non-infiltrating carcinoma was defined as ductal carcinoma *in situ* and lobular carcinoma *in situ*. Infiltrating carcinoma comprised infiltrating ductal and lobular carcinoma or other types of infiltrating carcinomas. Immunohistochemical staining of ER, PR and Her-2/neu were carried out in the Pathology department of our hospital. The scoring system for ER and PR concluded the proportion and intensity scores. Subsequently, staining results ranged from score 0 to 12, and scores of 1-12 with the nucleic staining of carcinoma cells were defined as positive. Her-2/neu was defined as negative for scores of 0-8 (namely 0, 1+ and 2+ in the Dako scoring system) and positive for strong membranous staining with scores of 9-12 (namely Dako score 3+). To examine whether the proportion of ER/PR$^+$ tumors differed by age, the patients were divided into 5 groups according to age: 23-34, 35-49, 50-64, 65-79 and 80-94 years. Patients treated with breast-conserving surgery (BCS) or with locally advanced breast cancer received irradiation. The dose to the whole breast was 50 Gy in 1.8-2.0 Gy per fraction, with a boost to the tumor bed in breast-conserving patients, while the dose to the chest wall and regional nodes was 50 Gy, as recommended for mastectomy patients. Patients with ER$^+$ and/or PR$^+$ diseases received adjuvant endocrine therapy for at least 3 years. Patients recorded as 'chemotherapy-given' were defined as patients who had received adjuvant chemotherapy for no less than 2 cycles. The majority of the elderly patients received cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or anthracycline-based chemotherapy, using the recommended dose and schedule. Among them, ~86% of the patients received ≥4 cycles and only 14% of the patients recieved a reduction in the dose owing to the side effects. Trastuzumab was not used in any of the patients.

Statistical methods. The date of surgery was used as the point of commencement for survival analysis. Relapse-free survival (RFS) was calculated from the date of surgery to the first evidence of disease recurrence (any site); all other patients were censored for progression at the date of the last visit without signs of progression or death. Overall survival (OS) was measured from the date of surgery until the patients succumbed to any cause or until the last follow-up. The significance of differences in categorical variables was evaluated using the Chi-square test and the significance of differences in continuous variables was evaluated using the Student's t-test. Cumulative RFS and OS were calculated using the Kaplan-Meier method (9). P<0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA).

Table I. The clinical characteristics of the patients in the case and control groups.

	Case (%)	Control (%)	P-value
No. of patients	594	657	
Mean age (years)	75.2±4.4	49.8±9.2	
Menarche age (years)	15.2±1.7	14.8±1.6	
BMI (kg/m²)	24.65	23.96	
Parous			
No	516 (97.9)	640 (98.3)	0.620
Yes	11 (2.1)	11 (1.7)	
Family history of breast cancer			
No	573 (96.5)	614 (94.5)	0.100
Yes	21 (3.5)	36 (5.5)	
Family history of other cancer			
No	535 (90.1)	551 (85.0)	0.008
Yes	59 (9.9)	97 (15.0)	
Pre-operative diagnosis	70	164	
Histology	29 (41.4)	110 (67.1)	0.001
Cytology	24 (34.3)	21 (12.8)	
Fiberoptic ductoscopy	12 (17.1)	18 (11.0)	
Lymph node biopsy	5 (7.1)	15 (9.1)	
Surgery	537	657	
Lumpectomy	14 (2.6)	8 (1.2)	0.001
Mastectomy	41 (7.6)	12 (1.8)	
MRM	412 (76.7)	503 (76.6)	
RM	67 (12.5)	37 (5.6)	
Lumpectomy + axillary	3 (0.6)	74 (11.3)	
Reconstruction	0 (0.0)	23 (3.5)	

BMI, body mass index; MRM, modified radical mastectomy; RM, radical mastectomy.

Results

Clinical features. Table I shows the clinical characteristics of patients in the two groups. A total of 1,251 breast cancer patients were selected, 594 patients aged ≥70 years were in the case group and 657 patients aged <70 years were in the control group. The median age was 75.2±4.4 years (range 70-92) in the case group and 49.8±9.2 years (range 23-69) in the control group. Age of menarche, parous status and BMI index were similar in the two groups. No significant difference was found in the proportion of breast cancer in first-degree relatives between the two groups; however, elderly patients showed a relatively lower frequency of other cancer history compared to young patients (9.9 vs. 15%, P=0.008). Only 11.8% (70/594) of the elderly patients received a pre-operative pathological diagnosis, <25% (164/657) of the patients in the control group. A cytology diagnosis and fiberoptic ductoscopy were more commonly used in the elderly, while a histology diagnosis, such as core needle biopsy (CNB), was preferred in young patients (P<0.001). A total of 537 patients in the case group and 657 in the control group had detailed surgery records and

Table II. The pathological and biological characteristics of the patients in the case and control groups.

	Case (%)	Control (%)	P-value	OR (95% CI)
Histological subtype	573	647		
Carcinoma *in situ*	53 (9.2)	74 (11.4)	0.327	
Microinvasive	18 (3.1)	15 (2.3)		
Invasive	502 (86.7)	557 (86.1)		
Lymph node	552	600		
Negative	428 (77.5)	347 (57.8)	<0.001	0.40 (0.31-0.51)
Positive	124 (22.5)	253 (42.2)		
Tumor size	575	616		
≤2 cm	162 (28.2)	194 (31.5)	0.023	-
2-5 cm	337 (58.6)	370 (0.1)		
>5 cm	76 (13.2)	52 (8.4)		
Estrogen receptor	453	487		
Negative	160 (35.3)	194 (39.8)	0.160	-
Positive	293 (64.7)	293 (60.2)		
Unknown	141	170		
Progesterone receptor	438	484		
Negative	184 (42.0)	208 (43.0)	0.790	-
Positive	254 (58.0)	276 (57.0)		
Unknown	156	173		
Her-2	434	482		
Negative	389 (89.6)	410 (85.1)	0.047	1.52 (1.02-2.26)
Positive	45 (10.4)	72 (14.9)		
Unknown	160	175		
p53	411	466		
Negative	179 (43.6)	159 (34.1)	0.004	1.50 (1.13-1.96)
Positive	232 (56.4)	307 (65.9)		
Unknown	183	191		

Her-2-negative is immunohistochemical (IHC) -,+ or ++; Her-2-positive is IHC +++. OR, odds ratio; CI, confidence interval.

the difference in surgery types was significant. Approximately 10% of the elderly patients had no axillary treatment (lumpectomy or mastectomy alone), a percentage that was higher as compared to the control group (P<0.001). Furthermore, the proportion of breast-conserving surgery performed (lumpectomy ± axillary, 3.2%) was lower in the case group (P<0.001).

Tumor stage. Tumor stage distribution was generally different in the two groups. We defined stages 0, I and II as 'early stage' and stages III and IV as 'advanced stage'. The percentage of early-stage patients was significantly different between the two groups: 89.4% in the case vs. 83.6% in the control group (P=0.004, OR=1.70, 95% CI 1.18-2.33).

Pathological and biological characteristics. Table II shows the pathological and biological characteristics of the two groups. The two groups had similar histological subtypes. Patients in the case group had more LN-, Her-2-and p53-negative diseases (P<0.05). The percentage of large tumor size (>5 cm) in the case group was higher than that in the control group, 13.2 vs. 8.4% (P=0.023). No difference was noted in ER and PR status (P=0.16 and 0.79, respectively). However, we found that the proportion of ER+ and hormone receptor

(HR)-positive tumors increased with increasing age (ER+ or PR+ defined as HR+). The overall ER+PR- or ER-PR+ proportion did not vary with age, while in the elderly patients we found a higher proportion of ER+PR+ and a lower proportion of ER-PR- diseases compared to patients aged <70 years (Fig. 1). Fig. 2 shows the distribution of HR and LN status according to age. Whatever the HR status proved to be, elder patients had less LN+ disease. For these LN- patients, only the HR+ proportion increased along with age.

Relapse-free and overall survival. The median follow-up time was 45.45 months in the whole cohort of 1,154 patients (case group 543 and control group 611). Fig. 3 shows that elderly patients exhibited a decreased survival curve compared to younger patients, the 5-year RFS was 77% in the elderly patients and 86% in the young patients (P=0.01) and the 5-year OS was 82 and 93%, respectively (P=0.028; the RFS and OS were adjusted by tumor size, LN, HR, Her-2 and adjuvant therapy).

Prognostic factors. The elderly patients had more ER+ and LN- diseases; thus the prognostic factors were analysed to determine whether the factors affected RFS and OS (Fig. 4). The 5-year RFS was 81% in ER+ patients, 73% in ER- (P=0.05),
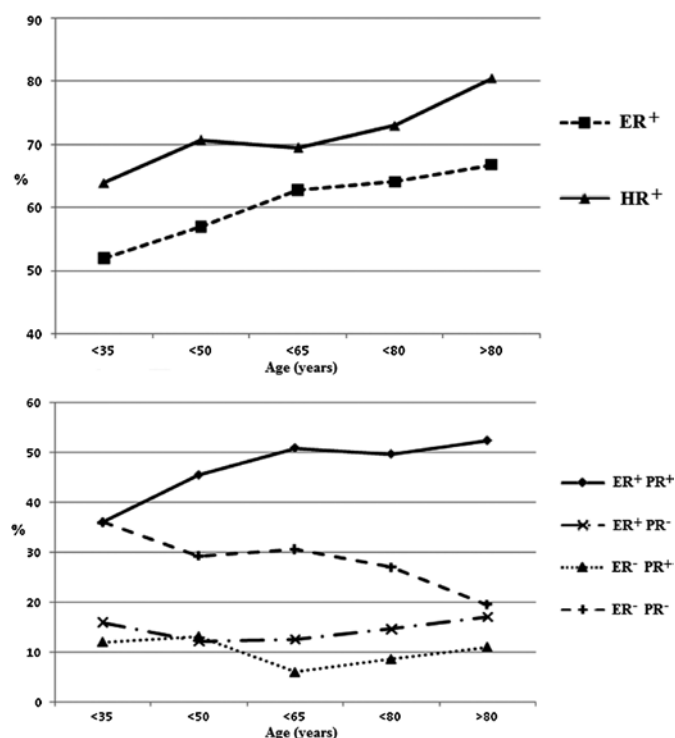
Figure 1. Age-related changes in hormone receptor expression status (the patients were divided into five groups according to age: 23-34, 35-49, 50-64, 65-79 and 80-94 years).
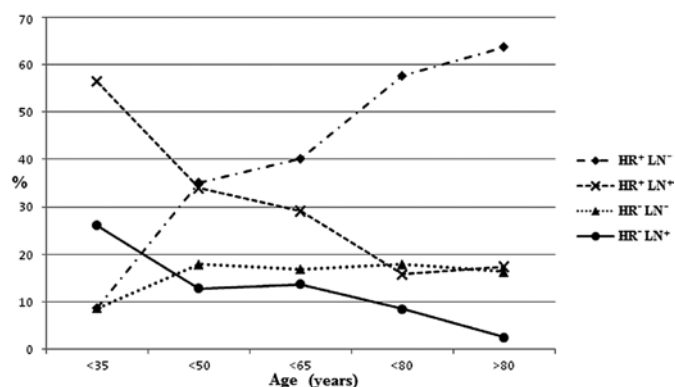

Figure 2. Age-related changes in the distribution of hormone receptor and lymph nodes status (the patients were divided into five groups according to age: 23-34, 35-49, 50-64, 65-79 and 80-94 years).

83% in LN⁻ and 63% in LN⁺ patients (P=0.000025). The OS of ER⁻ patients was lower than that of ER⁺ patients, although the differences were not statistically significant (P=0.075; Fig. 4B). LN⁻ patients had a higher OS, as shown in Fig. 4D (P=0.0001).

Adjuvant therapy. We investigated whether endocrine therapy and chemotherapy were beneficial for elderly patients. Fig. 5A and B shows that RFS and OS were significantly better in elderly patients that underwent endocrine therapy (P=0.01 and 0.05, respectively). Patients undergoing chemotherapy had a decreased 5-year RFS compared to patients undergoing omitted chemotherapy (70 vs. 83%, P=0.048). Patients without chemotherapy may therefore have a better survival, although a statistically significant impact on OS was not demonstrated (P=0.10).

Discussion

The WHO Health Report shows that the average life expectancy is 76 years in developed countries and 67 years in developing countries, and the median life expectancy of Chinese women is 74 years (10). Therefore, in modern society, clinicians are likely to increasingly treat cancers in the elderly. However, the definition of 'elderly' remains controversial. Gennari and Audisio suggested that the term 'elderly' involves patients who are 70 years of age or older since this age limit represents a milestone beyond which older people are found (11). A survey by the Breast International Group (BIG) comprising 277 oncologists from 28 countries indicated that 70 years is the cut-off age commonly used to define a patient as elderly (12). Accordingly, this retrospective analysis assumed 70 years to be the cut-off age.

No differences were detected in menarche age, parous status, BMI index or family history of breast cancer between the case and control groups. However, we found a significantly lower proportion of family cancer history among the elderly patients, which is in agreement with Pappo *et al* (13). The differences in pre-operative pathological diagnostic methods were also confirmed by our study. As older patients were less healthy, a histology biopsy, such as CNB, was often substituted by a cytology exam prior to surgery. Therefore, when treating the elderly, patient evaluation should be closely assessed.
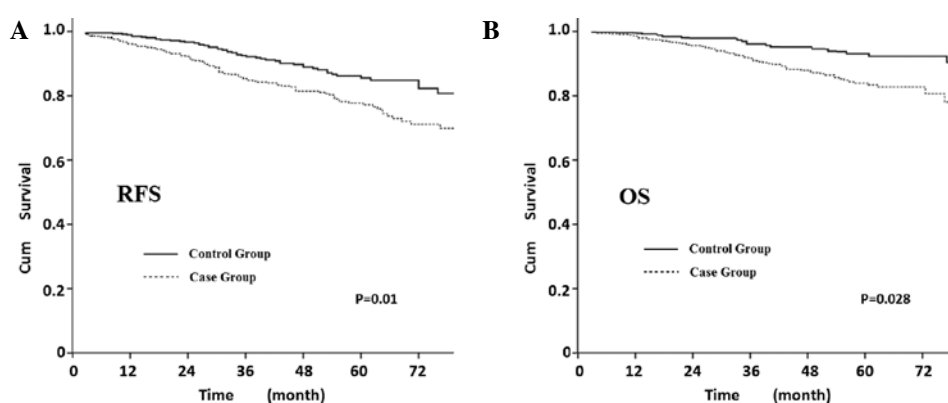

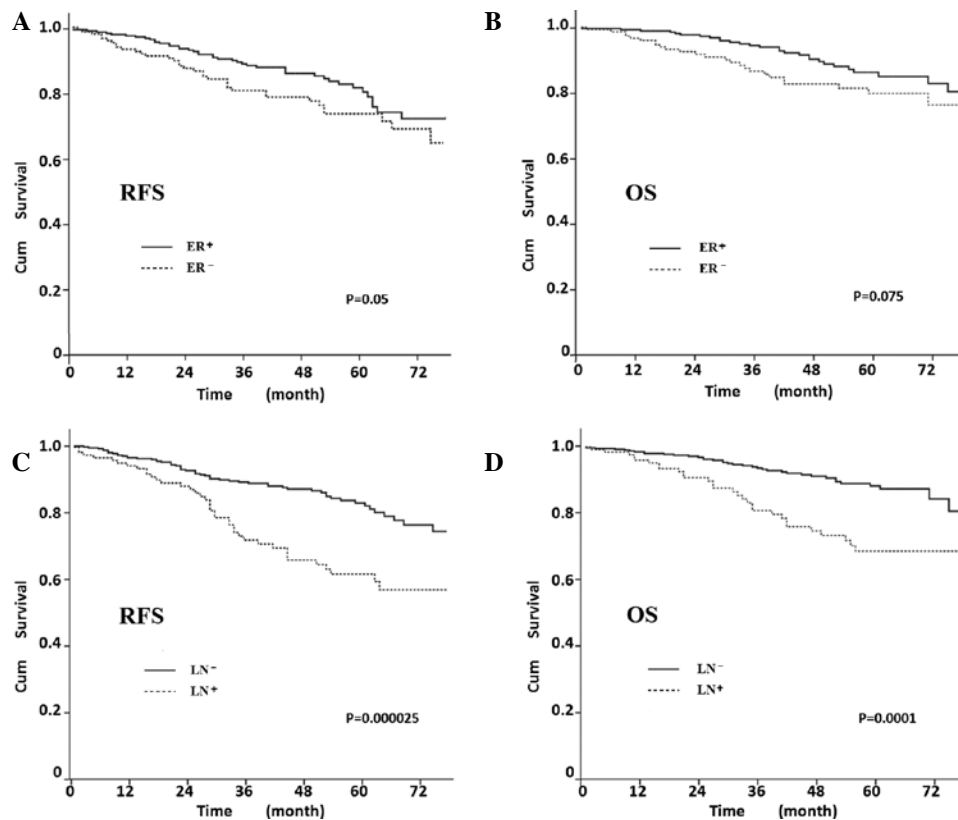Figure 3. Disease-free and overall survival in the case and control groups.

Figure 4. Relapse-free and overall survival according to estrogen receptors and lymph node status in the elderly group.
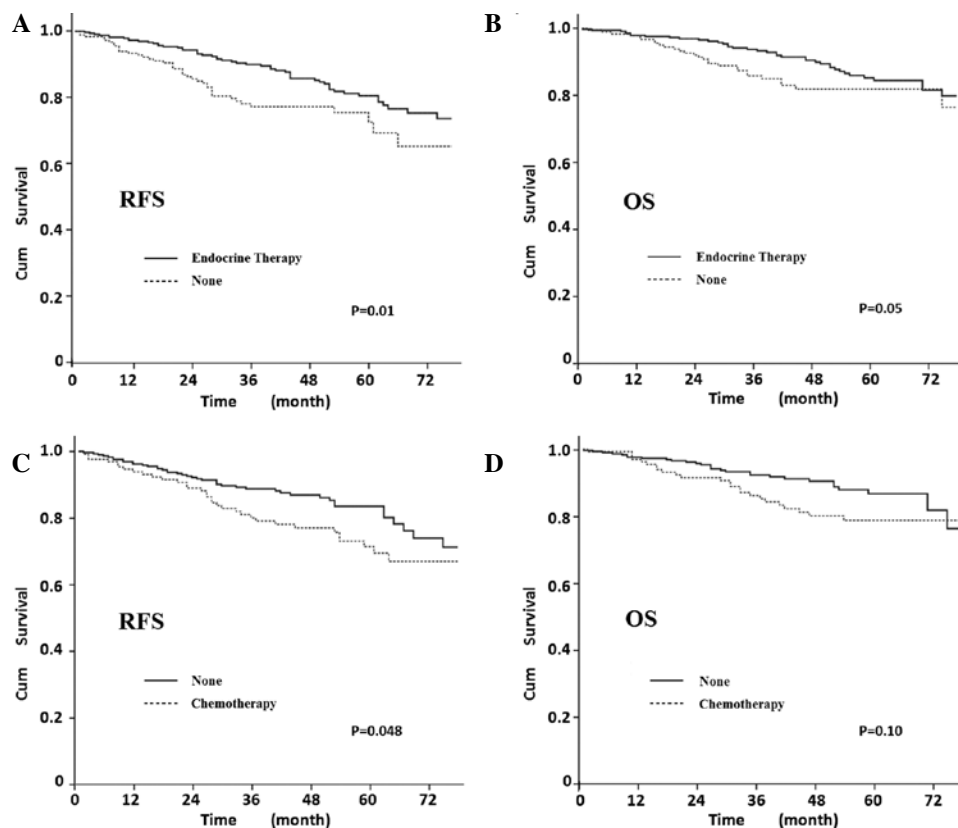

Figure 5. Relapse-free and overall survival according to adjuvant endocrine therapy and chemotherapy in the elderly group.

A detailed baseline assessment, such as Comprehensive Geriatric Assessment (CGA) and Multidimensional Geriatric Assessment (MGA), may help to evaluate the performance status and guide the decision-making process (14-16).

Recent advances in anesthesia resulted in a significant decrease in operative mortality proportions for fit older women with breast cancer. Additionlly, extremely elderly patients are safely treated by breast cancer surgery with a low incidence of perioperative complications (17). We performed different types of surgery for elderly patients (Table I). However, the case group received less axillary treatment or BCS than the control group, as was the case in the study by Pierga *et al* (18). The axillary dissection rate decreases with age (19); a rate which was half in the over 70-year age group when compared to younger patients (20). Whether older patients require LN evaluation is often debated (21). Studies have suggested that older patients with HR+ breast cancer or tumors smaller than 3 cm and who are clinically node-negative omit node dissection or may be offered a sentinel LN biopsy (22,23).

Another reason for omitting axillary dissection is that breast cancer in older women often presents indolent features: a higher frequency of ER/PR+, lower expression of HER-2 and p53 proteins, low proliferation rate, low S-phase or low Ki67 and a well-differentiated tumor (24-26). The present study showed a favorable tumor profile in the elderly patients, as well as a lower expression of Her-2 and p53 and an increased proportion of ER+ and PR+ tumors with age increase. In our series, the ER+PR- and ER-PR+ the proportion of tumor profiles was stable in all age groups, although the elder patients exhibited more ER+PR+ and fewer ER-PR- tumors. The distribution of HR and LN status also varied with age. In patients less than 35 years of age with LN- diseases, the HR+ and HR- proportions were similar, but were lower than those in LN+ diseases. However, the favorable prognosis subtype HR+LN- proportion increased markedly with age, while the LN- proportion markedly decreased.

Although the case group had a high proportion of HR+, LN- and early-stage disease, RFS and OS decreased. We hypothesized that i) the higher rate of large tumor size in the case group may lead to an early relapse, as suggested by Truong *et al* who found that older patients had similar or higher local recurrence risks, particularly patients with tumors larger than 5 cm or with more than 4 positive nodes (27); ii) more co-morbid diseases of older women may result in more deaths, as reported by Louwman *et al* who noted that 14% of the newly diagnosed patients at age 70-79 and 22% of patients older than age 80 suffered from more than two concomitant conditions (28); iii) more elderly patients received less than 'optimal' treatments (29,30) and under-treatment may strongly decrease outcome (31).

The present study focused on whether ER and LN status had an impact on survival in the case group. Fig. 4 shows that LN status was the most significant prognostic predictor in elderly patients, and markedly affected RFS and OS (P<0.001). The significant decrease in the survival of LN+ patients suggested the importance of axillary surgery in elderly patients. Inadequate axillary treatment may lead to an increased rate of regional failure (32) and LN status is reported to be a predictor of distant metastasis in elderly breast cancer patients (33). ER status also predicts recurrence in elderly patients, and although OS was not statistically different, ER+ had a better survival curve.

The efficacy and utility of adjuvant systemic therapy in elderly patients remains uncertain, particularly chemotherapy (34,35). Thus, it remains to be determined whether elderly patients exhibited the same sensitivity to systemic adjuvant therapy. In our data, elderly patients with suitable functional status received chemotherapy. However, these patients exhibited a lower RFS and OS. It is likely that elderly patients were less sensitive to chemotherapy, and, as Livi *et al* reported, chemotherapy was correlated with a lower survival rate (36). Nevertheless, this result may be due to the fact that only patients with worse prognostic factors received chemotherapy and that the majority of elderly patients in our study received CMF or anthracycline-based chemotherapy, which had a low effect and high cardiac toxicity (37,38). Tamoxifen (TAM) is as effective for reducing the risk of recurrence and cancer-related mortality in women over 70 years of age as it is for younger women (39). The majority of the ER+ patients in the case group received TAM as adjuvant endocrine therapy. We found that TAM significantly improved RFS and OS in the elderly group with good tolerance.

In conclusion, elderly breast cancer patients had favorable features. However, the co-morbid diseases and under-treatment of elderly patients resulted in lower RFS and OS in the elderly patients. ER+ and LN- were favorable prognostic predictors. Careful evaluation should be considered when recommending adjuvant system therapy.

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