Original Research Article

Increasing Mortality in Korean Patients With Breast Cancer: High Mortality Rate in Elderly Breast Cancer Population Due to Suboptimal Treatment and Other Diseases

Cancer Control
Volume 28: 1–9

DOI: 10.1177/10732748211037914
journals.sagepub.com/home/ccx
SAGE

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Abstract

Background: The incidence of breast cancer in Asia, including Korea, has rapidly increased. Each country has shown different clinical features. This study presents a comprehensive understanding of breast cancer in different age groups in Korea and determines potential measures for improving patient survival.

Methods: Patients diagnosed with invasive breast cancer stages I to III with available clinicopathologic and follow-up data were included in the study. Kaplan–Meier survival graphs were generated for each group and compared using log-rank test. The hazard ratio for each risk factor was calculated using the Cox regression model and the 95% confidence interval.

Results: The final cohort included 833 patients with a mean age of 51.3±11.3 years (range, 22–89 years), and 191 (22.9%) of them were aged >60 years. Patients aged ≥60 years had worse overall survival (OS) and distant disease-free survival than those aged <60 years. Although no difference was observed in the tumor biology, elderly patients showed significant differences in practice patterns: they tended to undergo mastectomy (40.2% vs 62.8%, $P<0.001$), did not receive the standard chemotherapy (88.4% vs 69.3%, $P < 0.001$), and had a higher risk of developing second primary cancer or diseases other than breast cancer (1.2% vs 6.8%, $P < 0.001$), which significantly correlated with poor survival in elderly patients.

Conclusion: Less-than-the-standard treatment of care or development of a second primary disease resulted in poor prognosis in elderly patients in Korea. A multi-institutional and multinational study is warranted to elucidate the clinical features of breast cancer in Asian patients.

Keywords

breast cancer, elderly patients, overall survival, poor prognosis, suboptimal treatment

Received January 21, 2021. Received revised April 26, 2021. Accepted for publication July 9, 2021.

Introduction

Breast cancer among Asians has been associated with a distinct shape of age-specific incidence rate patterns and an early age-onset compared with that among the Western population, and each Asian country or region has also shown different features.[1–5] For example, Korean patients who have a lower incidence of breast cancer compared with other Asian patients are commonly diagnosed with breast cancer during

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the 5th to 6th decades, with a decreasing incidence after the age of 65 years, showing an inverted U-shaped incidence by age.[1,2] Although most of the Asian countries showed a lower incidence of breast cancer than Western countries,[1,5] in some countries, such as Singapore, or the Philippines, the incidence rate increased rapidly and peaked during the 7th decade, which was similar to the pattern of Western patients with breast cancer; in other regions, such as Hong Kong and Shanghai, the incidence rate did not decrease even after it reached the peak.[1,5] Another distinctive feature among Korean patients with breast cancer is that mortality due to breast cancer showed a continually increasing trend, which is a unique pattern, unlike that in Western countries.[6]

Elderly patients with breast cancer have worse outcomes than their younger counterparts.[7,8] The number of elderly patients with breast cancer increases with age, while that of young people remains the same (Figure 1).[9] However, an incidence lower than that of middle-aged women and complicated medical histories prevent elderly patients in Korea from actively participating in clinical trials or studies, resulting in a paucity of information.[8,10]

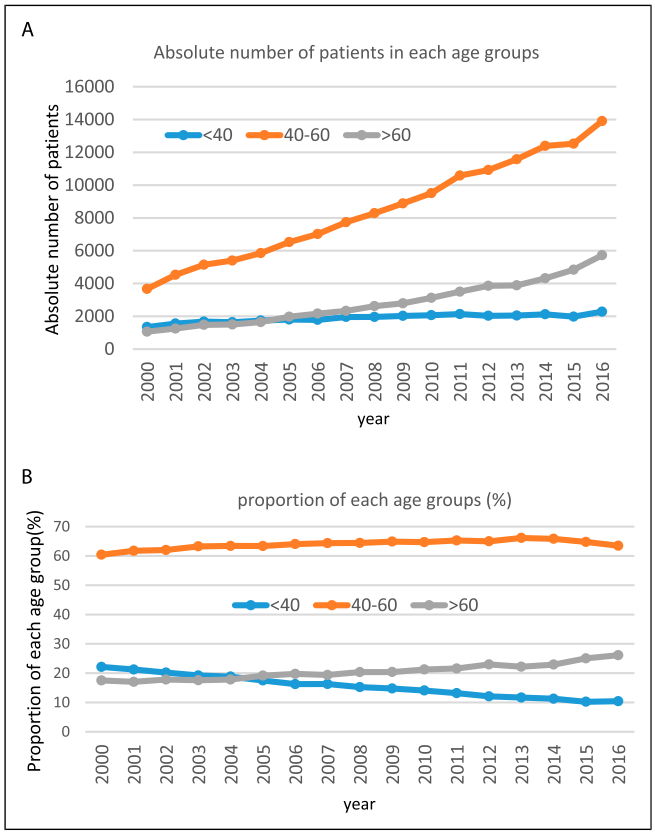

Figure 1. Annual number of patients with breast cancer in Korea. (A) Absolute number of patients stratified in three age groups, namely, <40 years, 40–60 years, and >60 years, for the period 2000–2016 and (B) Proportion of patients in each age group from 2000 to 2016, elderly patients were more in number than patients <40 years. Modified data from K-indicator. http://kosis.kr/statisticsList/statisticsListIndex.do.[2]

Considering that most of them are still able to perform most of the activities of daily living and are highly functional in performing regular exercises, a comprehensive understanding of breast cancer in elderly patients will help offer reasonable options on how to deal with the disease in women moving into their 7th decade and beyond. Our study aimed to investigate the significant risk factors of breast cancer in elderly patients and determine the factors that contribute to their clinical course. We also aimed to investigate the relationship between age and disease prognosis in each clinical subtype defined by estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2) status and disease stage.

Materials and Methods

Study Cohort: Inclusion and Exclusion Criteria

Patients of all ages who were diagnosed with invasive breast cancer stages I to III and completed their surgical treatment between 2000 and 2013 at Wonju Severance Hospital, Yonsei University, Wonju, Korea, were included in the study. Patients were included even if they had a less-than-the-standard treatment plan or had failed to complete their planned treatment. Patients who only received a diagnosis and refused any treatment and those who received hormonal therapy without appropriate staging workup and/or follow-up were excluded from the analysis.

Collection of Data: Clinicopathologic, Laboratory, and Survival Data

A retrospective chart review of the clinicopathologic features, including patients' age, tumor size, presence of axillary lymph node metastases, hormonal receptors, and HER2 status of the tumor, and treatment information was performed. Data on ER, PR, and HER2 status were extracted from pathological reports, mainly from immunohistochemical (IHC) staining reports. Tumors were classified as ER-positive if there was more than 10% reactivity until 2010, and the threshold for ER positivity was decreased to ≥1% from June 2010 onward. HER2 expression status was routinely assessed by IHC staining, and in situ hybridization was used for evaluation when IHC staining showed borderline results. IHC surrogates defined the clinical subtypes as ER-positive/HER2-negative, HER2-positive, or triple-negative breast cancer (TNBC). The patients were divided into two age groups after comparing the three groups representing the pre-, peri-, and post-menopausal periods.[7,11,12] The patients were initially divided into three groups to analyze the effect of age on survival: those aged ≤40 years, those aged 40–60 years, and those aged ≥60 years old.[7,11] The Kaplan–Meier curves were generated for each of the three groups to determine the optimal cutoff value for survival analysis, and another Kaplan–Meier curve was generated to confirm the difference in survival between two groups after the patients were divided into two age groups.

Planned Treatment

Planned treatment and its completeness were determined from the medical records, including prescription history. Treatment was selected based on the Health Insurance Review and Assessment (HIRA) guidelines, provided by the government-run health insurance system in Korea. In detail, systemic treatment differed according to the breast cancer subtype and tumor-node-metastasis (TNM) staging; the appropriate scheme was defined for each subtype and TNM status: ER-positive breast cancer, anti-hormonal treatment for all cases and chemotherapy if the tumor was ≥1 cm and/or nodal metastasis; TNBC, chemotherapy if the tumor was ≥1 cm and/or node-positive disease; and HER2-positive disease, chemotherapy if tumor was ≥1 cm and/or node-positive disease was present. A separate analysis of each treatment, anti-hormonal therapy and chemotherapy, was performed except HER2 targeted agents because trastuzumab was not covered by the HIRA guidelines until 2010, and most patients did not receive target agents as treatment for their primary condition. Suboptimal treatment was determined based on either the duration of hormonal therapy or the total amount of drugs in the case of chemotherapy. Hormonal treatment was considered insufficient if it lasted ≤2 years.[13] Chemotherapy was considered in sufficient if applied in ≤85% of the recommended amount.[14,15] A drug switch, according to the protocol, for example, from selective estrogen receptor modulators to aromatase inhibitors or vice versa, was not considered as suboptimal treatment. Changing medication due to disease progression was not considered a suboptimal treatment, and patients' data were sorted on the day of the event. For patients with HER2-positive disease, suboptimal treatment with target therapy was not explored because trastuzumab was covered by the HIRA guidelines after 2010; since off-limit usage was illegal under the HIRA coverage system in Korea, target agents were not administered as treatment for their primary condition.

Statistical Analysis

The standardized definitions for efficacy end points criteria were used to define each endpoint (Online Supplementary Table).[16] The primary endpoint was overall survival (OS), described as the time from primary diagnosis to the date of death from breast cancer, non–breast cancer, or unknown causes. The secondary endpoints were, distant disease-free survival (DDFS), defined as any distant recurrence or death from breast cancer, non–breast cancer, or unknown causes. Kaplan–Meier graphs were generated and tested using the log-rank test to compare the survival. Cause-specific mortality rates were analyzed using Cox regression models to estimate the hazard ratios (HRs) with their respective 95% confidence intervals (CIs) as a measure of the association between age at diagnosis, subtype, and cause-specific mortality rates. In the subset analysis, the models also included planned adjuvant treatments. All tests were two-sided, and the significance level was set at 5%. The analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA).

Results

Worse Survival of Patients Aged ≥60 Years

A total of 833 patients were enrolled in the final cohort, with a mean age of 51.3 ±11.3 years (22–89 years) (Figure 2). Approximately 60% of patients (n = 508) were in their 5th to 6th decade; over 134 patients (16.1%) were aged <40 years, and 191 patients (22.9%) were aged >60 years, which was similar to the nationwide breast cancer incidence in Korea.[2,6,17] Patients were divided into three groups: those aged <40 years, those aged 40–60 years, and those aged >60 years. Kaplan–Meier graphs were generated to determine whether any of the groups had a different OS. They showed that only patients aged >60 years had a worse prognosis (Figure 3). Patients aged ≥60 years had worse OS and DDFS. They also tended to have worse invasive disease-free survival (IDFS), recurrence-free interval, or distant recurrence-free interval, with a weaker association. Further comparison of survival among the three age groups with Kaplan–Meier graphs was performed, suggesting that 60 years of age could be the appropriate cutoff value for further evaluation (Supplementary Figures 1 and 2). Patients aged ≥60 years were not different from those aged less than 60 years in terms of clinicopathologic factors except tumor size (Table 1). Although no difference was observed in terms of tumor biology, such as hormonal and HER2 status, the two groups showed a significant difference in practice pattern. The elderly patients had higher risk of undergoing more mastectomy (40.2% vs 62.8%, $P<0.001$) and lower chance of receiving standard chemotherapy (88.4% vs 69.3%, $P < 0.001$) (Table 1). The elderly patients also had a higher death rate from second primary cancer or any other life-threatening disease (1.2% vs 6.8%, $P < 0.001$) (Table 1).

Risk Factors Contributing to a Worse Prognosis

The Cox proportional hazard model showed T3 disease, presence of axillary lymph node metastases, negative ER, inadequate/fail-to-complete planned treatment, and second primary cancer or life-threatening events from any origin other than breast as independent significant risk factors (Figure 4). In the subgroup analysis, patients with ER-positive breast cancer were influenced by insufficient hormonal treatment (HR, 2.68; 95% CI, 1.46–4.91) but not insufficient chemotherapy (HR, 1.25; 95% CI, 0.57–2.73). On the contrary, patients with TNBC were influenced by insufficient chemotherapy (HR, 2.12; 95% CI, 1.02–4.34) (Figure 4B and 4C). OS and DDFS remained poor even after nodal status and breast cancer subtypes were adjusted (Figure 5). Elderly patients showed inferior survival in all subgroups, except in the subgroup with T3 disease or HER2-positive disease.

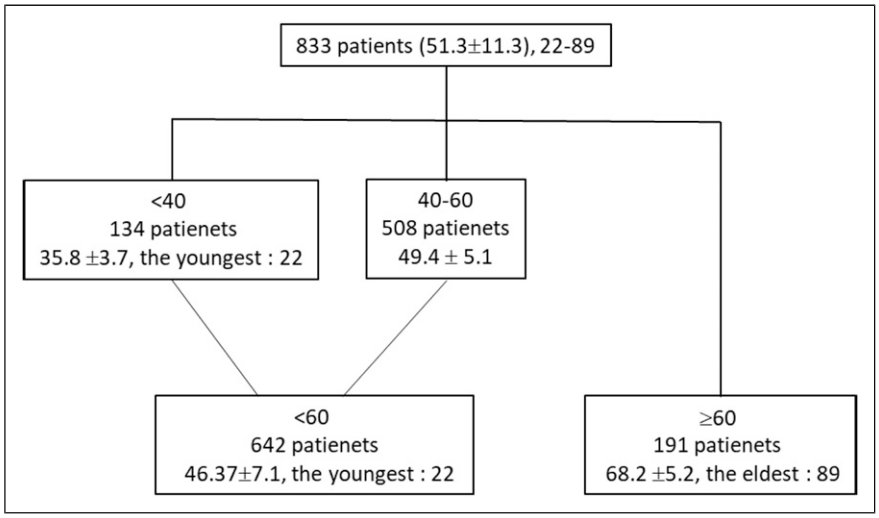

Figure 2. Study profile. In total, 833 patients are included, with a mean age of 51.3±11.3 years (range: 22–89 years). The patients are divided into three age groups: <40 years (n = 134), 40–60 years (n = 508), and >60 years (n = 191). The figure shows that most women in this cohort were diagnosed with breast malignancy in their 5th and 6th decades, which is consistent with the nationwide report of age distribution of patients with breast cancer in Korea.[1,2]

Discussion

Our study showed worse prognosis of elderly patients with breast cancer with around 50 years as the median age of breast cancer than that of younger patients. Unlike previous studies indicating the poor prognosis of younger patients,[18–21] younger patients in this cohort did not have an inferior prognosis compared with the middle-aged group. Most of the reviews discussing younger age groups were only limited to patients aged below 50 years and/or middle-aged group who have shown better survival than the younger age group and the elderly group, diluting the influence of age on prognosis.[18–21] Moreover, poor prognosis identified in extremely young patients with ER-positive breast cancer may be due to the inadequate control of estrogen because recent clinical trials using tamoxifen plus ovarian suppression and gene signature guided treatment and chemotherapy benefit, showed better survival than tamoxifen alone in premenopausal women, suggesting that inadequate control of estrogen had an impact on survival.[21–23]

Another reason for the poor survival of elderly patients could be the definition of survival used in this study. The primary endpoint of this study was OS, which was defined as the time from primary diagnosis to the date of death from breast cancer, non–breast cancer, or other reasons/unknown causes.[16] In contrast, other reviews regarding the poor prognosis of extremely young patients have used disease-free survival, which includes loco-regional recurrence and contralateral breast cancer.[18–21] OS is the least ambiguous and most clinically relevant endpoint.[16,24] On the contrary, disease-free survival cannot always serve as an early indicator of good or worse survival unless death over a more extended period is predicted.[16,24] It is generally accepted that distant recurrence (metastasis) triumphs over other events and is a threat to patient survival.[16] Hudis et al.[16] proposed the exclusion of ipsilateral recurrence of breast tumors, regional invasive recurrences, contralateral breast cancer, and all in situ carcinomas from the definition of DDFS because these events were potentially nonlethal and using a combined regional and distant endpoint would dilute the correlation with survival and weaken the discriminatory power of the analysis. However, OS can raise a couple of concerns: potential overstatement of poor prognosis from non–breast cancer–related events and diluting the effect of breast cancer–related loco-regional recurrence. Instead of OS with potentially exaggerated risk from non–breast-related diseases, breast cancer–specific mortality included only cases in which breast cancer was the leading cause. In this case, however, it may be difficult to distinguish a second primary cancer from a distant recurrence of the primary breast cancer or treatment-related disease. OS has the advantage of involving any life-threatening events, including invasive cancer, which might be related to the condition or its treatment.[16]

Multivariate analysis using the Cox hazard model showed that elderly patients had worse OS due to non–breast cancer–related reasons, such as less than standard treatment or second primary cancer, which is consistent with the findings of previous studies.[7] Suboptimal treatment could be one of the areas in which treatment outcome can be improved with a change in the perception of cancer and age. However, there are also caveats regarding the definition of under-treatment. For example, the recent coronavirus disease 2019 pandemic has prompted the clinicians to raise questions about the appropriate treatment for patients with limited capacity in a restricted situation, which could be necessary for elderly patients with limited medical capacity.[25] We defined insufficient treatment as

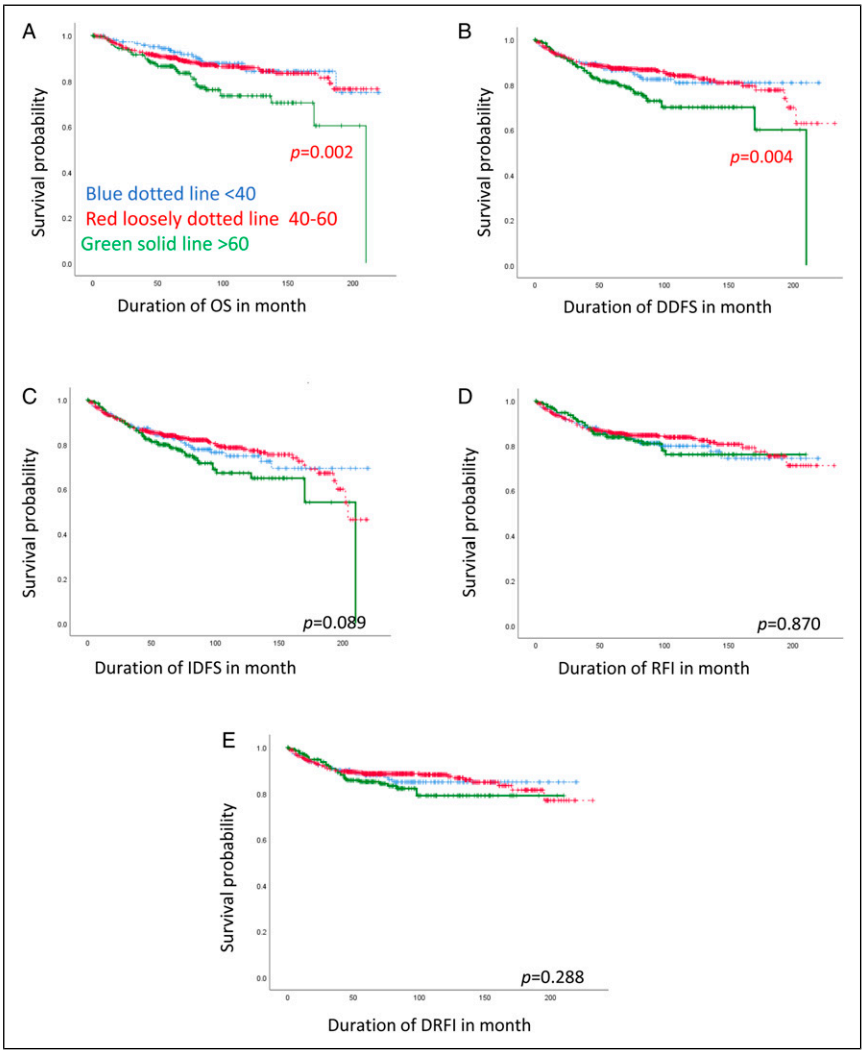

Figure 3. Kaplan–Meier curves. Caption: (A) overall survival (OS), (B) distant disease-free survival (DDFS), (C) invasive disease-free survival (IDFS), (D) recurrence-free interval (RFI), and (E) distant recurrence-free interval (DRFI). After stratification, the patients were placed in three age groups: <40 (blue), 40–60 (red), and >60 (green). Elderly patients show a significantly worse prognosis in OS and DDFS and a tendency for inferior IDFS.

treatment that cannot guarantee an established effect not less than 2 years for tamoxifen or not less than 85% of the total planned dose for chemotherapy was defined as sufficient treatment.[13,14] This was much less than that of the current standard[26] but had still a significant different influence on survival.

Elderly patients were affected from receiving less-than-the-standard chemotherapy and insufficient anti-hormonal treatment. However, each subtype had a different influence on treatment-related issues. Patients with ER-positive breast cancer were affected from receiving less than 2 years of anti-hormonal treatment but not from receiving less-than-the-standard chemotherapy (Figure 4B). By contrast, patients with TNBC were significantly affected by under-treatment with chemotherapy (Figure 4C). Given that the minimum treatment defined as 2 years of tamoxifen treatment or 85% of the total planned chemotherapy dose showed survival differences in ER-positive and TNBC patients, respectively, minimum treatment should be offered for relevant patient groups, regardless of their age. The elderly patients also had higher risk of undergoing mastectomy (40.2% vs 62.8%, $P < 0.001$) and less-than-the-standard chemotherapy (88.4% vs 69.3%, $P < 0.001$), even though they did not have worse clinicopathologic factors and had a smaller tumor, suggesting biased treatments were offered to this group.

This study has several limitations. We were unable to establish whether old age resulted in worse prognosis or whether aging simply reflects a higher risk of comorbidities. Recent research provides a scientific background supporting the different biological features according to age: proteomic analysis of plasma protein showed that there were about three peaks of change among the undulating modifications of protein and genetic data. Surveillance, epidemiology, and end

Table 1. Clinicopathological Characteristics of the Patients.

	Total (n, %)	Age <60 years (n, %)	Age >60 years (n, %)	*P*-value
T Stage				**0.009**
I	404 (48.5)	316 (49.2)	88 (46.1)	
II	354 (42.5)	258 (40.2)	96 (50.3)	
III	60 (7.2)	54 (8.4)	6 (3.1)	
Unknown	15 (1.8)	14 (2.2)	1 (0.5)	
N stage				0.873
0	531 (63.7)	409 (63.7)	122 (63.9)	
I	167 (20.0)	130 (20.2)	37 (19.4)	
II	61 (7.3)	46 (7.2)	15 (7.9)	
III	51 (6.1)	37 (5.8)	14 (7.3)	
Unknown	23 (2.8)	20 (3.1)	3 (1.6)	
ER				0.794
Positive	513 (57.3)	398 (62.0)	115 (60.2)	
Negative	281 (33.7)	213 (33.2)	68 (35.6)	
Unknown	39 (4.7)	31 (4.8)	8 (4.2)	
PR				0.457
Positive	477 (57.3)	374 (58.3)	103 (53.9)	
Negative	317 (38.1)	237 (36.9)	80 (41.9)	
Unknown	39 (4.7)	31 (4.8)	8 (4.2)	
HER2				0.757
Negative	618 (74.2)	480 (74.8)	138 (72.3)	
Positive	173 (20.8)	131 (20.4)	42 (22.0)	
Unknown	42 (5.0)	31 (4.8)	11 (5.8)	
Operation				**<0.001**
BCS	426 (51.1)	360 (56.1)	66 (34.6)	
MRM	378 (45.4)	258 (40.2)	120 (62.8)	
Other	29 (3.5)	24 (3.7)	5 (2.6)	
Planned Tx				
Hormonal Tx				0.781
Completed	364 (43.7)	283 (44.1)	81 (42.4)	
Undertreated	89 (10.7)	67 (10.4)	22 (11.5)	
Missing	80 (9.6)	63 (9.8)	17 (8.9)	
NA*	300 (36.0)	229 (35.7)	71 (37.2)	
Chemotherapy				**<0.001**
Completed	585 (70.2)	481 (74.9)	104 (54.5)	
Undertreated	50 (6.0)	25 (3.9)	25 (13.1)	
Missing	46 (5.5)	37 (5.8)	9 (4.7)	
NA*	152 (18.2)	99 (15.4)	53 (27.7)	
Death not related to breast cancer	19/752 (2.5%)	7/575 (1.2%)	12/177 (6.7%)	**<0.001**
Missing	81	67	14	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BCS, breast conserving surgery; MRM, modified radical mastectomy; Tx, treatment; NA, not applicable.
*systemic treatment was not indicated by the HIRA guideline.

results data also showed that the three groups of patients with breast cancer had different prognosis.[11,12] These epidemiologic data showed three different prognostic groups with an overall J-shaped effect of age, with increased mortality among the youngest group and even higher mortality among the elderly group.[7,11,12] We hope that further understanding of the molecular biology of aging and cancer will help elucidate this issue.

Another limitation is that we evaluated the planned treatment at the time of diagnosis, which is different from the current medical standard; furthermore, we were unable to analyze the data of patients with HER2-positive disease because they did not receive HER2-targeted agents mainly due to regulatory and reimbursement issues. Nevertheless, as the same guideline was applied to all patients, this meant that the same bias can occur in all patients. Under these circumstances,

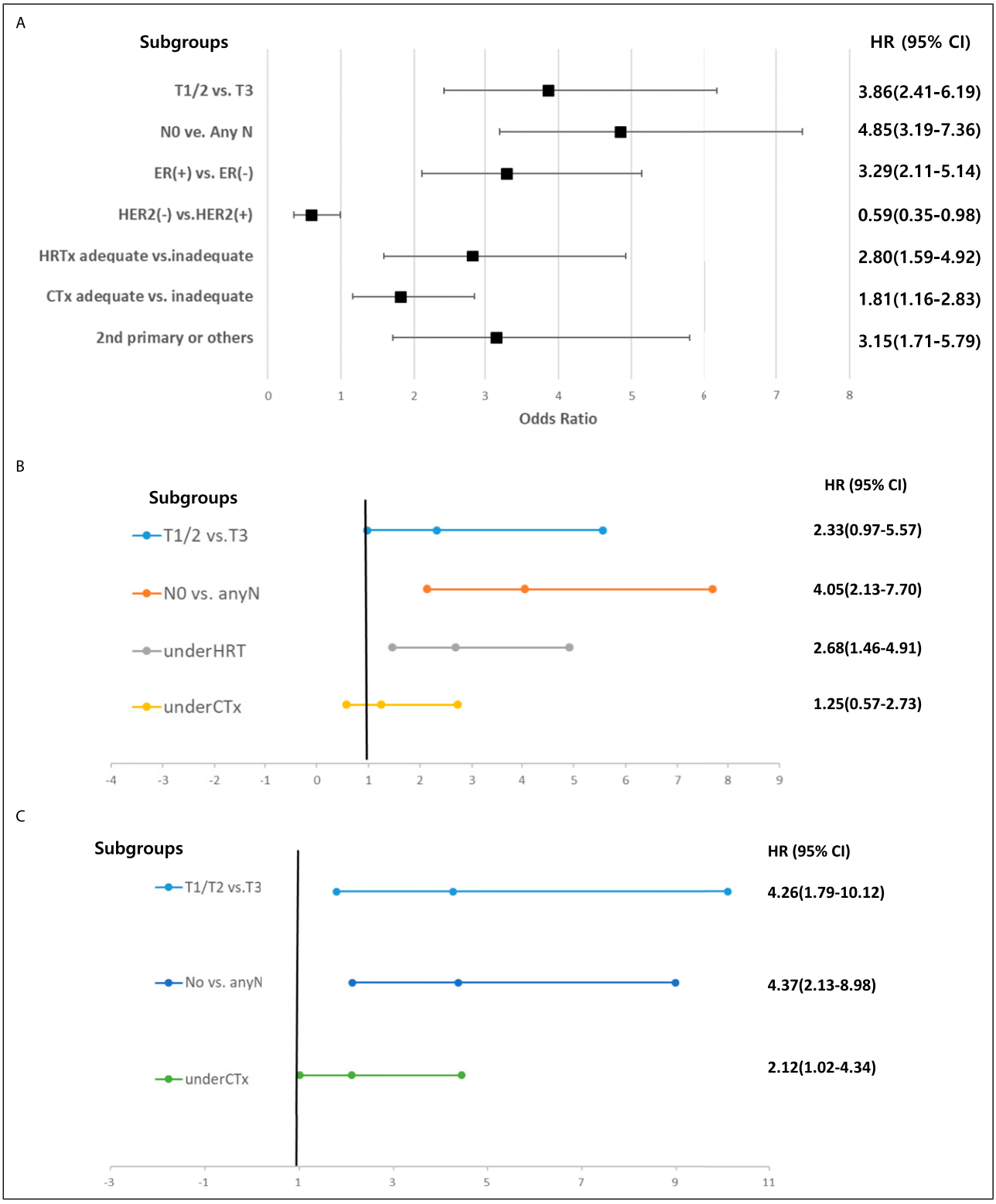

Figure 4. Risk factors contributing to worse prognosis in patients ≥60 years in (A) all patients, (B) patients with ER-positive HER2-negative disease, and (C) patients with TNBC patients. Cox hazard model was used and risk >1 indicates that the condition presented more risk. Analysis across the subtypes (A) showed large tumor size (T3), nodal metastasis, estrogen receptor-negative disease, inadequate hormonal treatment and chemotherapy, and second primary cancer, or any other life-threatening disease significantly contribute to poor prognosis. In subgroup analysis, ER positive patients (B) were influenced by insufficient hormonal treatment, not by chemotherapy. Patients with TNBC (C) were, however, significantly influenced by insufficient chemotherapy. ER: estrogen receptor, HER2: human epidermal growth factor receptor 2, TNBC: triple-negative breast cancer.

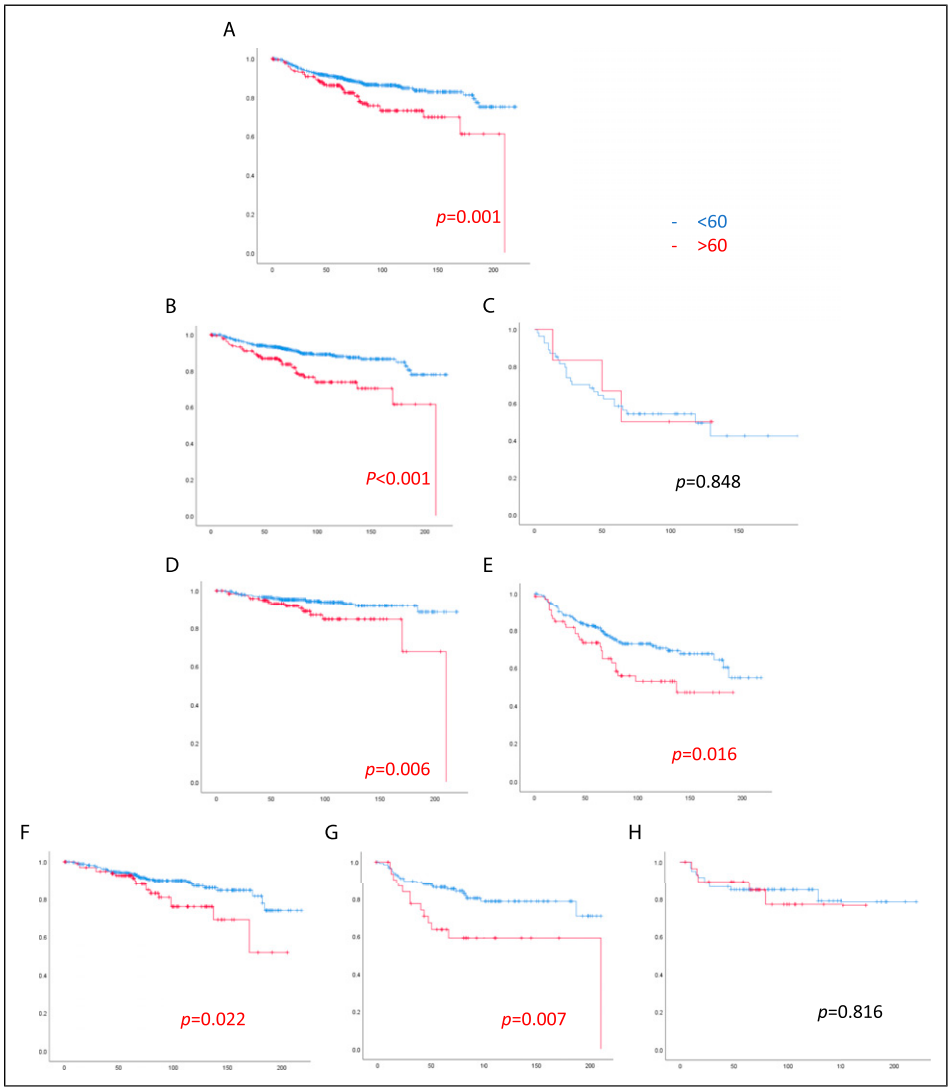

Figure 5. Overall survival stratified by pathological staging (B, C, D, and E) and clinical subtype (F, G, and H). The red line indicates elderly patients, and the blue line indicates younger patients. (A) Overall survival, (B) patients with T1/T2 disease, (C) patients with T3 disease, (D) patients with the node-negative disease, (E) patients with node-positive disease, (F) ER-positive HER2-negative, (G) TNBC, and (H) HER2-positive. T 1,2,3; tumor stages, ER: estrogen receptors, HER2: human epidermal growth factor receptor 2, TNBC: triple-negative breast cancer.

we found that less hormonal treatment affected the elderly patients with ER-positive disease and that chemotherapy influences the survival of elderly patients with TNBC.

Conclusion

Elderly patients with breast cancer experienced significantly worse OS when they received less-than-the-standard systemic treatment or developed second primary disease other than breast cancer, suggesting that adequate treatment is essential for this group. A nationwide, population-based study is warranted to provide a detailed understanding and help improve the survival of elderly patients with breast cancer.

Acknowledgments

We would like to thank all the patients who showed great courage against breast cancer and Editage (www. editage.co.kr) for providing English language editing assistance.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The Institutional Review Board for Medical and Health Research Ethics at Yonsei University Wonji College of Medicine approved this study (YWCM-2011-51).

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Supplemental Material

Supplemental material for this article is available online.

References

1. Shin HR, Joubert C, Boniol M, et al. Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. *Cancer Causes Control*, 2010. 21(11): p. 1777-1785.
2. Kang SY, Kim YS, Kim Z, et al. Breast cancer statistics in Korea in 2017: data from a breast cancer registry. *J Breast Cancer*, 2020. 23(2): p. 115-128.
3. Hayashi N, Kumamaru H, Isozumi U, et al. Annual report of the Japanese breast cancer registry for 2017. *Breast Cancer*, 2020. 27(5): p. 803-809.
4. Yoshimura A, Ito H, Nishino Y, et al. Recent improvement in the long-term survival of breast cancer patients by age and stage in Japan. *J Epidemiol*, 2018. 28(10): p. 420-427.
5. Lin CH, Yap YS, Lee KH, et al. Contrasting epidemiology and clinicopathology of female breast cancer in Asians vs the US population. *J Natl Cancer Inst*, 2019. 111(12): p. 1298-1306.
6. Jung KW, Won YJ, Kong HJ, Lee ES. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2015. *Cancer Res Treat*, 2018. 50(2): p. 303-316.
7. Johansson ALV, Trewin CB, Hjerkind KV, Ellingjord-Dale M, Johannesen TB, Ursin G. Breast cancer-specific survival by clinical subtype after 7-year follow-up of young and elderly women in a nationwide cohort. *Int J Cancer*, 2019. 144(6): p. 1251-1261.
8. Biskup E, Vetter M, Wedding U. Fighting diagnostic and therapeutic nihilism in the elderly with cancer. *Ann Palliat Med*, 2020. 9(3): 1324-1332.
9. K-indicator. http://kosis.kr/statisticsList/statisticsListIndex.do?menuId=M_01_01&parm TabId=M_01_01&parentId=D.1; D1.2; 101_11744.3; #SelectStatsBoxDiv. Accessed July 20th, 2020.
10. von Waldenfels G, Loibl S, Furlanetto J, et al. Outcome after neoadjuvant chemotherapy in elderly breast cancer patients - a pooled analysis of individual patient data from eight prospectively randomized controlled trials. *Oncotarget*, 2018. 9(20): p. 15168-15179.
11. Wang MX, Ren JT, Tang LY, Ren ZF. Molecular features in young vs elderly breast cancer patients and the impacts on survival disparities by age at diagnosis. *Cancer Med*, 2018. 7(7): 3269-3277.
12. Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*, 2008. 26(20): p. 3324-3330.
13. Ekholm M, Bendahl PO, Ferno M, et al. Two years of adjuvant tamoxifen provides a survival benefit compared with no systemic treatment in premenopausal patients with primary breast cancer: long-term follow-up (> 25 years) of the phase III SBII:2pre trial. *J Clin Oncol*, 2016. 34(19): p. 2232-2238.
14. Denduluri N, Patt DA, Wang Y, et al. Dose delays, dose reductions, and relative dose intensity in patients with cancer who received adjuvant or neoadjuvant chemotherapy in community oncology practices. *J Natl Compr Canc Netw*, 2015. 13(11): p. 1383-1393.
15. Weycker D, Barron R, Edelsberg J, Kartashov A, Lyman GH. Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. *Breast Cancer Res Treat*, 2012. 133(1): p. 301-310.
16. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*, 2007. 25(15): p. 2127-2132.
17. Hong S, Won YJ, Park YR, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2017. *Cancer Res Treat*, 2020. 52(2): p. 335-350.
18. Ahn SH, Son BH, Kim SW, et al. Poor outcome of hormone receptor-positive breast cancer at very young age is due to tamoxifen resistance: nationwide survival data in Korea–a report from the Korean Breast Cancer Society. *J Clin Oncol*, 2007. 25(17): p. 2360-2368.
19. Han W, Kim SW, Park IA, et al. Young age: an independent risk factor for disease-free survival in women with operable breast cancer. *BMC Canc*, 2004. 4: p. 82.
20. Kim EK, Noh WC, Han W, Noh DY. Prognostic significance of young age (<35 years) by subtype based on ER, PR, and HER2 status in breast cancer: a nationwide registry-based study. *World J Surg*, 2011. 35(6): p. 1244-1253.
21. Kim JK, Kwak BS, Lee JS, et al. Do very young Korean breast cancer patients have worse outcomes? *Ann Surg Oncol*, 2007. 14(12): p. 3385-3391.
22. Fu J, Wu L, Xu T, et al. Young-onset breast cancer: a poor prognosis only exists in low-risk patients. *J Cancer*, 2019. 10(14): p. 3124-3132.
23. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*, 2018. 379(2): p. 122-137.
24. Dignam JJ, Huang L, Ries L, Reichman M, Mariotto A, Feuer E. Estimating breast cancer-specific and other-cause mortality in clinical trial and population-based cancer registry cohorts. *Cancer*, 2009. 115(22): p. 5272-5283.
25. Spring LM, Specht MC, Isakoff SJ, et al. Case 22-2020: a 62-year-old woman with early breast cancer during the Covid-19 pandemic. *N Engl J Med*, 2020. 383(3): 262-272
26. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*, 2013. 381(9869): p. 805-816.