Peer Review File

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First External Peer Review

Reviewer A

Comment 1: *Patients with stage IV are included. These patients are absolutely different from patients with stage I-III regarding treatment. Patients with stage IV should be excluded from the study, or analyzed completely separately.*

Reply 1: We thank the reviewer for pointing out this issue. As you said, the prognosis of these two conditions is quite different. So we have now excluded patients with stage IV from the study (see Page 8, Line 142) and sincerely hope that our logic is now easier to follow with the new version. After excluding patients with stage IV, our main results did not materially change.
Changes in the text: Since we aimed to explore the associations between age at initial diagnosis and risk of recurrence or metastasis, patients with stage IV were also excluded from the study.

Comment 2: *The authors defined 'disease free survival' as the time from the first diagnosis of BC by surgery or puncture to recurrence and/or metastasis; however, 'Disease free interval' would be appropriate.*

Reply 2: We thank the reviewer for the suggestion. We have now replaced all "disease free survival" with "disease free interval" in the manuscript (see Page 9, Line 160; Page 9, Line 167; Page 12, Line 236).
Change in the text: Recurrence and metastasis information including distant metastasis sites, disease-free interval (DFI), endocrine therapy, targeted therapy, and chemotherapy after metastasis.

Comment 3: *As 'Molecular subtype' is determined pathologically, then 'pathological subtype' would be better.*

Reply 3: We thank the reviewer for the comment. However, we have defined pathological subtype as "Carcinoma in Situ", "Invasive Ductal", "Carcinoma", "Others Invasive", and "others". Since the molecular subtype is determined pathologically, we finally replaced "Molecular subtype" with "Molecular subtypes by post-operative pathology" (see Page 25, Table 1).

Comment 4: *Regarding 'surgery' in Table 3. What does 'No mastectomy' mean?*

Axillary node resection, only? What is the difference from 'Other'?

Reply 4: Thank you for your careful review. We apologize for the confusion by the previous version of the manuscript. We have now changed the surgery categories as "No", "Conservative surgery", and "Total mastectomy" in the current version (see Page 26, Table 2).

Reviewer B

Comment 1: As a general comment, the conclusions in the abstract lead to an inadequate tends to change treatments related to age. Maybe in a second lecture, and with the rest of the information described in the paper, the suitable conclusion is that because of the different treatment patterns applied (adjusted to patients conditions, and treatment decision-making of breast cancer) the prognosis is different, not necessary related only to age. So I suggest clarifying this question in the abstract.

Reply 1: We thank the reviewer for the valuable suggestion. We have clarified this question in the abstract, based on this helpful comment (see Page 4, Line 81).
Change in the text: Age at initial diagnosis is related to the clinicopathological characteristics and treatment pattern. Although the risk of site-specific metastasis varies by age, age is not an independent factor of total recurrence and metastasis. In accordance with current clinical practice guideLines for breast cancer, however, precised treatment shall be chosen personally for patients whose ages of initial diagnosis are different.

Comment 2: Table I with demographic characteristics adds no relevant information, so it could be deleted, just cited in the text, or even sent as supplementary material.

Reply 2: We thank the reviewer for the comment. We have now deleted Table 1 in the current version and added it to **supplementary material**.

Comment 3: The patients recruited mixed local recurrence with distant metastasis. The prognosis of these two conditions is quite different, so conclusions should be taken carefully.

Reply 3: We thank the reviewer for pointing out this issue. As you said, the prognosis of patients with different recurrence or metastasis status is quite different. So we have now excluded patients with stage IV from the study (see Page 8, Line 142) and sincerely hope that our logic is now easier to follow with the new version. After excluding patients with stage IV, our main results did not materially change.
Changes in the text: Since we aimed to explore the associations between age at initial diagnosis and risk of recurrence or metastasis, patients with stage IV were also excluded from the study.

Comment 4: *As the authors report, there are significant differences in the treatment among patients of different ages, so the assertion that "Our results indicated that age is an independent risk factor for poor prognosis in patients with breast cancer" shouldn't be restrictive. Even more, should be taken into consideration of the types of treatment more than the age of diagnosis. The statistical results obtained in SPSS must be analyzed, as the authors notice:*

"...under treatment might also contribute to worse prognosis among older patients, implying that in older patients with BC, low doses of chemotherapy or radiotherapy should be used with caution…"

Reply 4: We thank the reviewer for the suggestion. Our univariate analysis showed that compared with patients aged < 35 years, risk of recurrence or metastasis in those aged 55-64 years were significantly higher (HR=1.24, 95%CI: 1.04-1.47). We included age at initial diagnosis, stage, grade, molecular subtype, surgery, neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy, adjuvant endocrine therapy, and family history of BC in the multivariate analysis. Our results showed that only adjuvant chemotherapy and adjuvant endocrine therapy could reduce the risk of recurrence and distant metastasis by 64% and 36%, respectively ($HR_{adjuvant\ chemotherapy}$=0.36, 95%CI:0.24-0.54; $HR_{adjuvant\ endocrine\ therapy}$=0.64, 95%CI:0.46-0.90), and the effect of age was not significant anymore. We realized that the assertion that "Our results indicated that age is an independent risk factor for poor prognosis in patients with breast cancer"was indeed inappropriate, so we revised this problem in the current version as below (see Page 15, Line 316).

Changes in the text: Our results indicated that being 55 to 65 years old correlated with a higher risk of recurrence and metastasis among patients with BC, even though it was not an independent prognostic factor, which is inconsistent with current studies.

Comment 5: *Line 288: cite a Meta-analysis by Anders, supporting information obtained from that cite until Line 293. The paper cited is not a Meta-analysis, is a review of the epidemiology of breast cancer:*

"This article reviews the distinct epidemiology, etiology, clinicopathologic characteristics, biology, treatment strategies, outcomes, and psychosocial challenges of breast cancer before 40 years of age. Also included in this review are issues of familial breast cancer, fertility, premature menopause, breast cancer during pregnancy, and bone health. The US Surveillance, Epidemiology and End Results (SEER) database was the source of data for the tables and graphs presented here "

Reply 5: Thank you for your careful review. We apologize for our mistake by the previous version of the manuscript. We have replaced the "Meta-analysis" with "Review" in the current version (see Page 15, Line 305; Page 15, Line 310).

Changes in the text: A review of the epidemiology of breast cancer by Anders et.al…… However, there were few studies and sample sizes available for the 10-year local recurrence rate in this review.

Comment 6: *Line 293: …… "A pervious study"… should say.. a previous study…*

Reply 6: Thank you for your careful review. We have revised such spelling errors alike (see Page 15, Line 311).
Changes in the text: A previous study recruited 3,064 patients…

Comment 7: *In this Line is cited a study of EORTC trial 10853: two questions:*
1.- the paper is not cited in references, so we can´t exactly know which is. I think is this one: "Bijker N, Peterse JL, Duchateau L, Julien JP, Fentiman IS, Duval C, Di Palma S, Simony-Lafontaine J, de Mascarel I, van de Vijver MJ. Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol. 2001 Apr 15;19(8):2263-71."
2.- Trial 10853 has many papers related, and all of them are dealing with ductal carcinoma IN SITU, so we can´t apply those conclusions to advanced breast cancer

Reply 7: We thank the reviewer for pointing out this issue. We apologize for not citing references here. We totally agree that results of Trial 10853 may not apply to those conclusions to advanced breast cancer. In order to supporting our conclusion, we cited another paper here (Miles RC, Gullerud RE, Lohse CM, Jakub JW, Degnim AC, Boughey JC. Local recurrence after breast-conserving surgery: multivariable analysis of risk factors and the impact of young age. Ann Surg Oncol. 2012;19(4):1153-9.).
Changes in the text: A previous study recruited 3,064 patients who underwent breast conservation surgery between 1988 and 2001 at Mayo Clinic to evaluate the risk factors of local recurrence, and the results indicated that young age (< 40 years) increased the risk of local recurrence after breast-conserving treatment (see Page 15, Line 311).

Comment 8: *Line 295 says….. "shows that shows that…" I guess it should say only once: shows that.*

Reply 8: We thank the reviewer for pointing out this issue. We apologize for the mistake and we have revised this problem in the current version (see Page 15, Line 314)
Changes in the text: A study in China shows that both young (age < 35 years) and old (age≥65 years) breast cancer patients have poor prognosis

Comment 9: *The assertion (Line 320) that"After adjusting for TNM stage at initial diagnosis, grade, molecular subtype, family history of BC, and types of therapy, risk of recurrence and metastasis among elderly patients was not significantly higher than young patients"*
Seems to go against their own assertion in conclusions:
"age at initial diagnosis is related to the clinicopathological characteristics and treatment pattern, which could affect the prognosis of breast cancer. In accordance with

current clinical practice guideLines for BC, precise treatment shall be chosen personally for patients of different ages"

Reply 9: We thank the reviewer for the comment. We apologize for this confusion. We have changed our conclusion (see Page 17, Line 355).

Change in the text: Age at initial diagnosis is related to the clinicopathological characteristics and treatment pattern. Although the risk of site-specific metastasis varies by age, age is not an independent factor independent factors influencing the risk of total recurrence and metastasis. In accordance with current clinical practice guidelines for breast cancer, however, precised treatment shall be chosen personally for patients whose ages of initial diagnosis are different.

Second External Peer Review

Reviewer A
Comment 1:
- line 83 independent factors: is repeated and incongruous in plural with the sentence.
- this mistake is also in line 357

Reply 1: We thank the reviewer for your careful review. We apologize for the mistake and we have revised this problem in the current version (see Page 5, Line 88; Page 17, Line 362).
Changes in the text: ……age is not an independent factor influencing the risk of total recurrence and metastasis

Comment 2: Using the acronym of Hormone receptor as HR, it should be avoided to use the same for Hazard ratio (HR). This may lead to confusion: for example, even in the abstract, both acronyms are used.

Reply 2: We thank the reviewer for the suggestion. We have now deleted the the acronym of Hormone receptor to avoid the confusion (see Page 4, Line 73; Page 11, Line 215; Page 11, Line 218; Page 14, Line 281; Page 14, Line 301).