Author’s response to reviews

Title: AJCC 8th Edition Prognostic Staging provides no better discriminatory ability in prognosis than Anatomical Staging in triple negative breast cancer

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Reviewer 1 (Naoki Kanomata): The comparison of AJCC AS and PS for triple negative breast cancers was reported. This is an interesting manuscript.

Q1: In Statistical Analysis, "Cases with nuclear grade of grade III and IV in SEER cohort were both classified as G3 in PS system" AJCC uses histologic grade, not nuclear grade. The reanalyses using histologic grade should be done.

A1: Actually, the data exported from SEER was under histologic grade catalog, for example, grade III refers to "poorly differentiated", and grade IV refers to "undifferentiated/anaplastic". So we are sorry for the misuse of "nuclear grade" in the text. In the revised version of the manuscript, we have made the erratum as follow:

page 3, line 77: "Clinicopathologic data, including tumor histologic grade, pathologic T and N categories..."

page 3, line 98-99: "Clinicopathologic data including age at diagnosis, sex, year of diagnosis, primary site, histologic type, histologic grade, AJCC 7th edition stage group..."
Cases with histologic grade of grade III (poorly differentiated) and IV (Undifferentiated; anaplastic) in SEER cohort were both classified as G3 in PS system.

Q2: What histologic types were rare to be excluded in SYSUCC and PWH cases? Was only invasive carcinoma, NST evaluated?

A2: In the present study, rare histologic types of breast cancer, including ILC (n=8), medullary carcinoma (n=23), metaplastic carcinoma (n=11), mucinous carcinoma (n=5), invasive micropapillary carcinoma (n=2), apocrine carcinoma (n=4) and mixed carcinoma (n=3) were involved in the analysis in both SYSUCC-PWH cohort and SEER cohort. The detail is also shown in supplementary table 1. So In the revised version of the manuscript, we have deleted the words of "rare histological type of BC" in page 3, line 82-83.

Q3: In SEER cohort, were all histologic types used?

A3: As we mention above in A2, rare histologic types of breast cancer were involved in the analysis in both SYSUCC-PWH cohort and SEER cohort as shown in supplementary table 1. The exclusion criteria for SEER cohort described in page 3, line 101-102 do not include the rare histologic types of breast cancer, so no change has been made for Q3 in the revised version of the manuscript.

Q4: BRCA status would be interesting to be analysed.

A4: BRCA1/2 mutation and homologous recombination deficiency (HRD) are supposed to be important issues in assessing the prognosis for PARP inhibitors that have been approved for TNBCs. The present study aim to compare the discriminatory ability between AS and PS in TNBCs under the AJCC 8th criteria, which do not include BRCA1/2 or HRD status. Moreover, no adequate relevant data could be accessed in both cohorts for analysis. However, as we mention in the discussion part of the manuscript, "Upcoming studies should consider the incorporation of biologic factors that closely related to the development of novel clinical therapies in TNBCs, for example, Poly-ADP-ribose polymerase inhibitors (PARPi) including Olaparib or Talazoparib and platinum therapy may provided a significant benefit over standard chemotherapy with respect to progression-free survival for metastatic TNBCs with germline BRCA1/2 mutation". Besides, we also added Limitations part in the revised version of the manuscript with regard to the novel treatment issues in TNBCs as follow:

Q5: "No case was classified as anatomic stage IB in this cohort" seems strange. No cytokeratin immunohistochemistry was done?

A5: In the revised version of the manuscript, we stated that "Another limitation of the present study is that no case was classified as anatomic stage IB in SYSUCC-PWH cohort. In SEER cohort, we found that few cases of TNBC (1.3%) were classified as AS IB (T0NmiM0 and T1N1miM0). So it can be happened that no AS IB case was found in the SYSUCC-PWH cohort with a smaller sample size. This
may also due to the reluctance for pathologists to make the diagnosis of Nmi at the time of initial diagnosis. However, all the AS IB cases, regardless of the variety in histologic grade, are classified as the unchanged PS IB following the AJCC 8th criteria, which may not affect outcomes of the comparative study" in page 8, line 276-284.

Many thanks for the kindly suggestions.

Semir Vranic, MD, PhD (Reviewer 2): An interesting study trying to explore the relevance of novel (8th) AJCC TNM for two cohorts of triple-negative breast cancers. The authors found that novel staging did not provide better discriminatory ability in predicting TNBC patients' outcome compared with the classical anatomic TNM.

Q1: The findings from the present study are useful but I believe that the current staging will have to modified following novel treatment modalities such as immune checkpoint inhibitors and PARP inhibitors that have been approved for TNBC patients. However, in the cohorts presented in the current study, these novel treatment modalities were not used and consequently could not affect the outcome of the TNBC patients. The discussion paragraph on this should be expanded.

A1: We do agree that "Upcoming studies should consider the incorporation of biologic factors that closely related to the development of novel clinical therapies in TNBCs...", as we mention in the Discussion of manuscript (page 7, line 254-256). As a retrospective study, we enrolled TNBCs diagnosed at the time during 2005-2015 (SYSUCC, 2005-2013; PWH, 2002-2008; SEER, 2010-2015), when PARPi and immunotherapy were not widely approved for clinical practice and the predominant treatment of TNBC remains to be chemotherapy and radiotherapy, especially in Asian countries. BRCA1/2 mutation, homologous recombination deficiency (HRD), tumor infiltrating lymphocytes (TILs) and expression of PD-L1 (SP-142) in immunocytes are supposed to be important issues in assessing the prognosis of TNBCs for the immune checkpoint inhibitors and PARP inhibitors have been approved for TNBCs. However, we acknowledge that this issue should be noted in the Limitations of revised version of the manuscript as follow:

page 7-8, line 268-276: "One limitation of the present study is that we cannot acquire data regarding administration of PARPi and immunotherapy. As a retrospective study, we enrolled TNBCs diagnosed at the time during 2005-2015 (SYSUCC, 2005-2013; PWH, 2002-2008; SEER, 2010-2015), when PARPi and immunotherapy were not widely approved for clinical practice and the predominant treatment of TNBC remains to be chemotherapy and radiotherapy, especially in Asian countries. However, subsequent clinical trials, including EMBRACA[21] Trial, OlympiAD[22] Trial, PrECOG 0105 Trial [23] and IMpassion130 Trial[26], suggested the significant effects of novel treatment modalities especially for advanced TNBCs."

Q2: The authors should avoid using the confusing and long abbreviations in the abstract as these do not contribute to the clarity of it.

A3: Modifications have been made in the Abstract as follow:

page 2, line 31: "Clinicopathological data of TNBCs were identified in two involved institutions (SYSUCC-PWH cohort)."
A total of 611 and 31941 TNBCs were identified in two cohorts. No significant difference was observed in C index between AS and PS models for disease-specific survival (DSS), progression-free survival (PFS) or overall survival (OS) in either cohort.

Our findings demonstrated that prognostic staging system did not provide better discriminatory ability in predicting TNBCs prognosis than anatomic staging system.

Q3: Some minor typo errors should be fixed (e.g. discussion, not discussion, etc.).

A3: We are sorry for the typing errors. In page 6, line 191, we have fixed the subheading as "Discussion".

Many thanks for the kindly suggestions.

Naila Irum Hadi, M.D., MPhil (Reviewer 3):

Q1: This work shows that PS did not provide prognostic validity as compared to AS in TNBC. This observation seems controversial as some recent papers have shown that PS provided more accurate prognosis than AS.

Please see the following references:

1. Li et al, 2019 "The prognostic value of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system in triple-negative breast cancer".
2. Wang et al, 2018 "Evaluation of the prognostic stage in the 8th edition of the American Joint Committee on Cancer in locally advanced breast cancer: an analysis based on SEER 18 database".
3. Weiss et al, 2018 "Validation study of the American Joint Committee on Cancer eighth edition prognostic stage compared with the anatomic stage in breast cancer".
4. Luo et al, 2019 "Validation of the Prognostic Significance of the Prognostic Stage Group According to the Eighth Edition of American Cancer Joint Committee on Cancer Staging System in Triple-Negative Breast Cancer: An Analysis from Surveillance, Epidemiology, and End Results 18 Database". This needs to be properly explained in the Discussion which is lacking this particular aspect.

A1: Expansion has been made in the Discussion of revised version of the manuscript in regard of the references mentioned above.

Weiss, et al.[6] found that 13.6% BC patients could not be assigned to a prognostic stage due to the presence of N1mi disease in patients with tumors larger than T1 or uncategorized combinations of T and N categories with grade and HR and HER2 status. Some subsequent changes had been made and demonstrated in the AJCC 8th Edition Updates and Corrections, that N1mi disease in patients with T2, T3 and T4 cancers includes N1mi. In the present study, all TNBCs were perfectly assigned to a proper prognostic stage according to the criterion.

These findings are consistent with previous study by Liu, et al[8]. On the contrary, contradictory studies by Li, et al.[7] and Luo, et al.[19] indicated that the PS system displayed a more optimistic prognostic stratification and predictability than traditional AS system. However, Li, et al.[7] applied a earlier version of AJCC 8th criterion without subsequent corrections in a small sample cohort including stage IV disease. They also excluded special types of invasive breast cancer, and no relevant statistical methods had been applied to further assess and compare prognostic ability of
the two staging systems. Luo, et al.[19] used the goodness-of-fit test, included statistics as −2likelihood, AIC, and BIC, to describe the prediction capability of the two competing staging systems in TNBCs and found that new version of AJCC staging system were higher than before. However, they also mentioned that statistics such as AIC and BIC are not convertible to a clinical meaningful relevance. The calculation of the C-index at different time points did not show significant differences in the two competing stage systems, which is in line with our observations.

Q2: In inclusion/exclusion criteria also mention type of surgery, chemotherapy, radiotherapy etc.
A2: The data referring to the exact type of surgery, chemotherapy, radiotherapy cannot be acquired from SEER database. We stated in the revised version of the manuscript that: "Clinicopathologic data including age at diagnosis, sex, year of diagnosis, primary site, histologic type, histologic grade, AJCC 7th edition stage group (T, N, M), survival months, cause-specific death classification, treatment information, such as surgery, chemotherapy and radiotherapy, were collected." in page 3, line 98-101.

Q3: Abstract: Page 3; lines 15 & 16 - Why DSS is repeated twice?
A3: "DSS" has been changed to "OS" in the revised version of the manuscript as: "No significant difference was observed in C index between AS and PS models for disease-specific survival (DSS), progression-free survival (PFS) or overall survival (OS) in either cohort."

Q4: Prognostic stages could not be assigned due to presence of micro metastasis (pN1mi in T1, T2 & T3) in lymph nodes of patients with tumor size more than 2 cm or due to uncategorized combinations of T & N categories with tumor grade and HR / HER2 status. What did the authors do in such cases?
A4: We mention in the revised version of the manuscript that "Weiss, et al.[6] found that 13.6% BC patients could not be assigned to a prognostic stage due to the presence of N1mi disease in patients with tumors larger than T1 or uncategorized combinations of T and N categories with grade and HR and HER2 status. Some subsequent changes had been made and demonstrated in the AJCC 8th Edition Updates and Corrections, that N1mi disease in patients with T2, T3 and T4 cancers includes N1mi. In the present study, all TNBCs were perfectly assigned to a proper prognostic stage according to the criterion." in page 6, line 214-221.

Q5: Page 4; lines 29-32 - Reference 9 seems incorrect as it refers to HER2 testing in breast cancer. Page 4; lines 33 & 34 - Reference for HER2 status required.
A5: References have been corrected and added in page 3, line 89 and line 91.

Q6: Kindly mention the limitation(s) of your study.
A6: Please see the revised version of the manuscript (page 7-8, line 268-284): "One limitation of the present study is that we cannot acquire data regarding administration of PARPi and immunotherapy. As a retrospective study, we enrolled TNBCs diagnosed at the time during 2005-2015 (SYSUCC, 2005-2013; PWH, 2002-2008; SEER, 2010-2015), when PARPi and immunotherapy were not widely approved for clinical practice and the predominant treatment of TNBC remains to be chemotherapy and radiotherapy, especially in Asian countries. However, subsequent clinical trials, including EMBRACA[21] Trial, OlympiAD[22] Trial, PrECOG 0105 Trial [23] and IMpassion130 Trial[26], suggested the significant effects of novel treatment modalities especially for advanced TNBCs. Another limitation of the present study is that no case was classified as anatomic stage IB in SYSUCC-PWH cohort. In SEER cohort, we found that few cases of TNBC (1.3%) were classified as AS IB (T0NmiM0 and T1N1miM0). So it can be happened that no AS IB case was found in the SYSUCC-PWH cohort with a smaller sample size. This may also due to the reluctance for pathologists to make the diagnosis of Nmi at the time of initial diagnosis. However, all the AS IB cases, regardless of the variety in histologic grade, are classified as the unchanged PS IB following the AJCC 8th criteria, which may not
affect outcomes of the comparative study."
Many thanks for the kindly suggestions.