

Peer Review File

Article information: <http://dx.doi.org/10.21037/tcr-20-2379>.

Reviewer A

Comment 1: Line 62: “patients with bone metastases had a quite good prognosis”. Please, specify that the “good” prognosis is in comparison to other sites of metastases and not referred to the overall population of breast cancer patients (which includes early-stage ones who never experience disease relapse)

Reply 1: Thanks for your valuable comments and suggestion. We have modified our text as advised.

Changes in the text: Page 6, Line 73-78.

Comment 2: Lines 64-66: a comment on bone targeting agents (i.e. bisphosphonates, denosumab) should be added, since their introduction in breast cancer clinical practice has significantly improved both SRE rates and patients’ quality of life (D’Oronzo S et al, Journal of Bone Oncology 2018);

Reply 2: Thanks for your valuable comments and suggestion. we added some data about bone targeting agents as advised.

Changes in the text: Page 6, Line 82-89.

Comment 3: The methodological approach is not clear; did the author perform a longitudinal (i.e. prospective) evaluation of early-stage BC patients, who did or did not develop bone metastases during the follow-up? If so, please, specify this in the method and state the median follow-up time of patients for each sub-group. If not, the definition of “risk factors” or “significant predictors” of bone metastases is inappropriate.

Reply 3: Thanks for your valuable comments. Our research was a retrospective study. We added some new data about median follow-up time of patients for each studying group. And we have modified the words about “risk factors” or “significant predictors” as advised.

Changes in the text: Page 11, Line 211-212.

Comment 4: Moreover, the clinical stage of patients whose data were analyzed is not

clear; were the subjects in the “BM NO” group all stage IV? If so, what kind of distant metastases they had? Otherwise, did this group include both metastatic and not metastatic patients?

Reply 4: Thanks for your valuable suggestion. Our study registered M1 stage IV breast cancer patients with distant metastases, and the distant metastatic sites of “BM NO” group patients were brain, lung, liver or distant lymph nodes. We added new data in the inclusion criteria and Table 1.

Changes in the text: Page 8, Line 134-137. Table 1

Comment 5: Several expressions are inappropriate and should be rephrased; for instance, “complete metastatic sites” and “single-source breast cancer” (line 101), “associated significantly” (line 126), “lager” (line 134), “simple BMs” (line 141), “friendly nomogram” (line 179), etc.

Reply 5: Thanks for your valuable suggestion. “single-source breast cancer” is the official expression in SEER database, it means primary tumor. Other expressions have been modified as advised.

Changes in the text: Page 8, Line 135-136; Page 10, Line 180-181; Page 11, Line 212.

Comment 6: Lines 141-142 (Results): the authors state that “Breast cancer patients with simple bone metastases had a better prognosis than other metastatic breast cancer patients”. Please, describe survival outcomes of these groups of patients.

Reply 6: Thanks for your valuable suggestion. We added median overall survival time of these groups of patients as advised.

Changes in the text: Page 11, Line 214-217.

Comment 7: the comparison with TAILORx data looks inappropriate and, once again, makes it hard to understand what kind of patients were included in this analysis; were they early-stage or metastatic subjects? TAILORx had a totally different aim to the present study and should not be described in support of its findings.

Reply 7: Thanks for your valuable comments. Our study all included stage IV breast cancer patients. TAILORx trial was to evoke the idea of whether 21 gene testing can be performed for patients with bone metastases in the same situation and further precise treatment. And we have modified our text as advised.

Changes in the text: Page 14-15, Line 329-354.

Comment 8: Lines 223-230: this statement is quite risky, in consideration of recent data from ASCO 2020 (J Clin Oncol 38: 2020 suppl; abstr LBA2) and further literature on this topic which discourages surgical approaches in stage IV patients, except for palliative purposes.

Reply 8: Thanks for your valuable comments and suggestion. We have modified our text as advised and added recent data from ASCO 2020 .

Changes in the text: Page 16, Line 358-370.

Comment 9: References should be improved, by adding more recent publications on this topic.

Reply 9: Thanks for your valuable comments and suggestion. We added some new references as advised.

Changes in the text: References.

Comment 10: Minor comments:

-Abstract: please, define “SREs” at their first appearance in the text (line 34)

-Results: please, replace “seer” with “SEER” (line 144)

-Line 153: “statistically significant to bone metastases”. Please, add “correlated” or “associated with”.

Reply 10: Thanks for your valuable comments. We have modified our text as advised.

Changes in the text: Page 4, Line 31; Page 11, Line 218; Page 12, Line 247.

Reviewer B

Comment 1: My major concern is that data presented in Table 1 suggests that approximately half of patients did not had surgery of primary breast tumor, which is quite strange. In L164 authors refer to unresectable breast lesion. Does this mean diagnosed in stage IV instead? Please clarify since this was found to be prognostic and used for following analysis.

Reply 1: Thanks for your valuable comments and suggestion. We registered M1 stage IV breast cancer patients in our study. The SEER database provided the patients

information based on the first diagnosis, so it is not weird that the approximately 50% M1 stage IV breast cancer patients included in our study lose the opportunity for surgery when first diagnosed. As shown in logistic regression analysis and nomogram, surgery was an independent prognostic factor for incidence of bone metastasis. Patients without surgery were more prone to bone metastasis. We have modified “unresectable breast lesion” to “primary breast site without surgery” that could be easier to understand in the text.

Changes in the text: Page 12, Line 261-262.

Comment 2: L62-66: These two sentences are quite confusing; please clarify between the good prognosis of BC with BM in comparison with other sites, and the impact on OS or 5y-OS and morbidity if BM are detected.

Reply 2: Thanks for your valuable comments. We have modified our text as advised.

Changes in the text: Page 6, Line 73-78.

Comment 3: L67-70: The rational for the study could be more precise, and the fact the BC subtype is the most important prognostic factor for risk of BM is not clear.

Reply 3: Thanks for your valuable comments. We added data about BC subtype in our text as advised.

Changes in the text: Page 6, Line 101-103.

Comment 4: L77-78: What the authors mean with good prognosis in “Based on the comprehensive treatment and good prognosis, it’s difficult to collect data of patients diagnosed with stage IV breast cancer, which limits further research”?

Reply 4: Thanks for your valuable suggestion. We have modified our text as advised.

Changes in the text: Page 7, Line 112-114.

Comment 5: L147-149: better to present metastatic rate before BM specific rate

Reply 5: Thanks for your valuable suggestion. We have modified our text as advised.

Changes in the text: Page 11, Line 206-208.

Comment 6: L141: prognosis data must be presented here, and if possible compare BM-only, visceral only, BM+visceral

Reply 6: Thanks for your valuable suggestion. We added median overall survival time of these groups of patients as advised.

Changes in the text: Page 11, Line 214-217.

Comment 7: L178: BM decrease OS so please rephrase this sentence

Reply 7: Thanks for your valuable suggestion. We have modified our text as advised.

Changes in the text: Page 13, Line 281-282.

Comment 8: The manuscript requires style, grammar and format revision, few examples:

a) L50-52: Refer to AUC for values

b) L60: BC has...

c) L77: it is (not it's)

d) L99-L101: From 2014 to 2020... was retrospectively studied...

e) L104: avoid "we got"

f) L105: include description of abbreviations

g) L124: larger

h) L143: SEER

i) L141: simple bone metastases should be replaced by bone-only metastases for example

j) Table 1: Demographic and clinicopathologic instead of Baseline; SEER instead of Seer (but remove SEER or add to development as it is also from SEER); one decimal is enough; T and N are not stage, this would be for TNM; what is T0?; include histologic types in the abbreviations.

k) Table 2: include histologic types in the abbreviations.

l) L179: avoid friendly

m) L203: Rephrase "We have heard a different voice about the prognosis of ILC"

Reply 8: Thanks for your valuable suggestion. We have modified our text as advised. J) We added explanation in our text as advised. T0 patients are defined as not having evidence of a primary tumor, according to the TNM system, in both AJCC versions 6 and 7.

Changes in the text: a) Page 5, Line 51-52; b) Page 6, Line 70; c) Page 7, Line 114; d) Page 8, Line 145; e) Page 9, Line 155; f) Page 9, 153-155; g) Page 10, Line 187-188;

h) Page 11, Line 218-219; i) Page 11, Line 212-213; j) Table 1; Page 9, Line 156-160;
k) Table 2; l) Page 13, Line 283; m) Page 15, Line 316.