Manuscript ID : 35399

Title : Survival analysis based on HER2 status in stage II-III gastric cancer

Dear Damian Garcia-Olmo, MD, PhD, Editor-in-Chief, WJG

Thank you very much for your valuable review of our manuscript. All comments were very helpful in revising and improving this report, and we did our best to respectfully follow your detailed advice. Heeding closely to the constructive comments suggested by the Editor and the reviewers, we have addressed each issue in a point-by-point manner below.

We also confirm that all of the authors have read and agreed with the revised manuscript.

Thank you again for considering our work for publication in this prestigious journal.

Best regards,

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Reviewer(s)' Comments:

Reviewer: 1

Comments to the Author

General:

Clear and quite accurate work . The statistics were performed on a fair number of patients. Conclusions agree with those of other works in the literature.

Specific:

1. Gastric cancer is not the second leading cause of cancer-related deaths in the world, but the third as shows the latest work of Ferlay J et al. of 2015, which you mentioned in the paper before.

→ We corrected the sentence as follows (page 4/lines 3-4). In addition, gastric cancer is the third leading cause of cancer-related deaths worldwide.

2. In Patients Characteristics and in Discussion the number of 834 patients is reported instead of 384.

→ In Patients Characteristics, we corrected the number (834→384). However, in Discussion, 834 was correct. The total number of patients we found to have HER2 status that included stages I-IV was 834. Among them, stage II or III patients was 384.

Reviewer: 2

Comments to the Author

General:

Manuscript entitled " Survival analysis based on HER2 status in stage II-III gastric cancer." mainly discussed HER2-positive patients had inferior OS and RFS. Stage II-III HER2-positive patients might be potential candidates for targeted therapies involving trastuzumab. The draft aimed to investigate human epidermal growth factor 2 (HER2) overexpression and validate its prognostic effect in stage II-III gastric cancer. Clinical data from 384 patients were analyzed. HER2-positive patients had inferior OS and RFS. Stage II-III HER2-positive patients might be potential candidates for targeted therapies involving trastuzumab. The data suggested that trastuzumab or other humanized monoclonal antibodies might play a similar role in an adjuvant setting in patients with stage II-III HER2-positive gastric cancer. And further studies are needed. And stage II-III patients exhibiting HER-2/neu amplification might be potential candidates for new adjuvant therapies involving the use of humanized monoclonal antibodies.

Specific:

1. There is a small question to discuss with the authors as follows. In general, some experimental study had better to be cited to support the authors` hypothesis, for example the literature like Biomaterials, 2012, 33:5349.

→ Following your suggestion, we inserted an additional sentence and reference (page 11 / lines 25-26). Although some experimental studies have been conducted, further studies are required.

Reviewer: 3

Comments to the Author

General:

Survival analysis based on HER2 status in stage II-III gastric cancer. Jang Ho Cho, et al This manuscript is very unique because of analyzing stage II-III gastric cancer depending on HER2 overexpression or not, however, I need the elucidation of the following points.

Specific:

#1 From Fig.2, OS was more dependent on HER2 overexpression in Stage III, but not in Stage II (Fig.2A). Thus, the analysis can be done according to stage II or III.

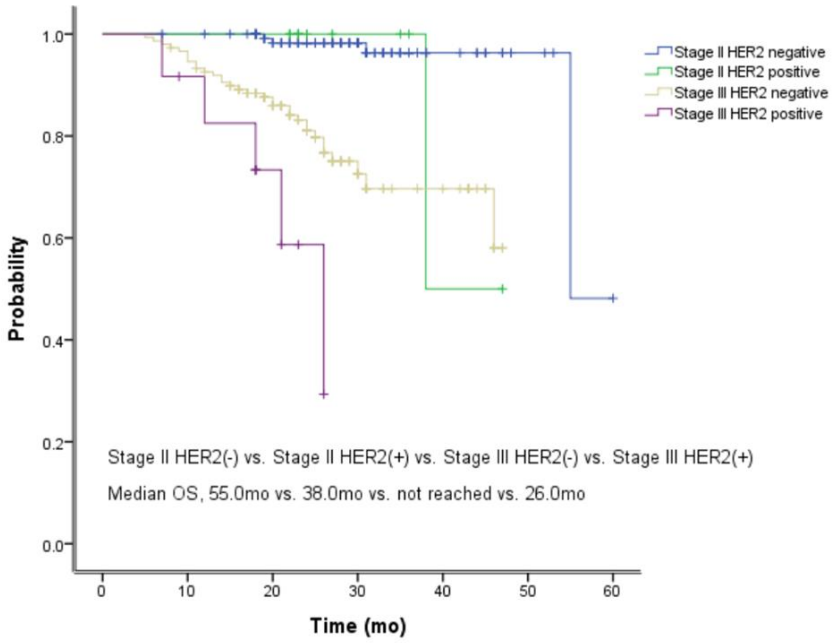
➔ We fully agree with your comment, and have corrected the sentence in the Result section (page 8).

Stage II HER2-negative patients had improved OS compared to stage II HER2-positive patients, although the difference was not statistically significant (HR: 0.21; 95% CI: 0.05-0.86; p = 0.30; Fig. 2a).

➔ We aimed to show numerical difference between HER2-negative and HER2-positive groups in stage II gastric cancer, although the difference was not statistically significant. In stage III, median OS was significantly prolonged in HER2 negative group.

#2 Fig.3 can be corrected to each OS in stage II and III who received adjuvant chemotherapy.

➔ We inserted additional Figure 3B to follow your suggestion.

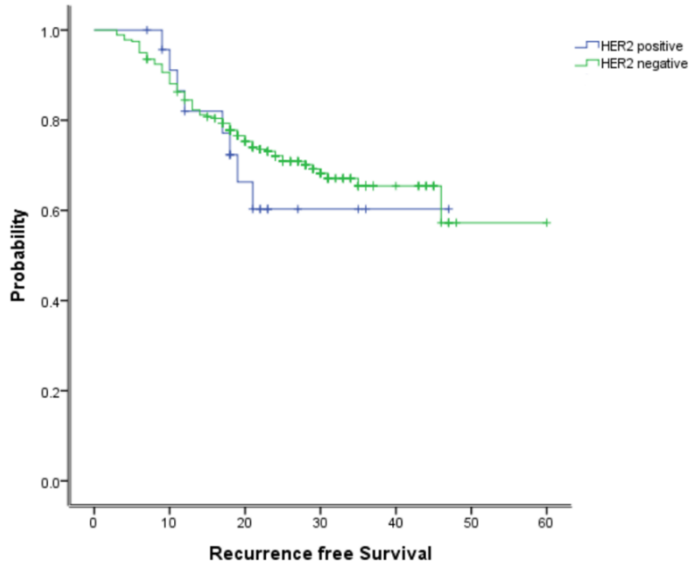


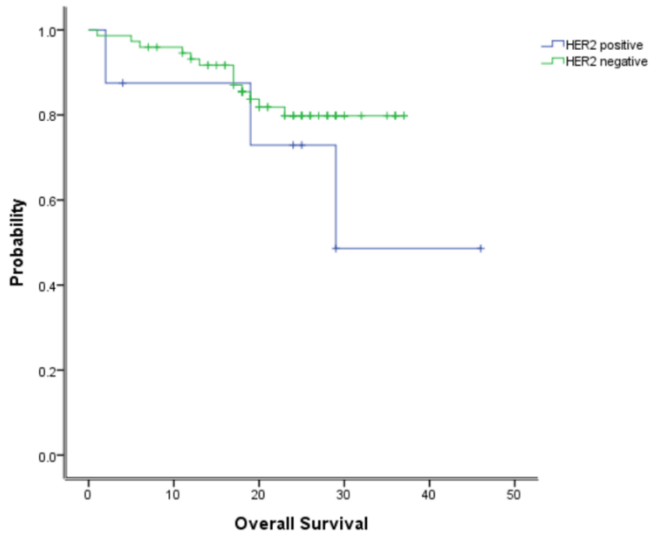
#3 I would like to know prognostic factor specifically such as HER2 overexpression and adjuvant chemotherapy in stage II or III. Hence, the following analysis should be addressed; OS in Stage II or III who did not receive adjuvant chemotherapy. OS in stage II or III who received adjuvant chemotherapy. RFS in Stage II or III who did not receive adjuvant chemotherapy. RFS in stage II or III who received adjuvant chemotherapy.

- ➔ As we mentioned above, OS was prolonged in HER2-negative group for stage II-III patients who received adjuvant chemotherapy, compared to HER2-positive group (55.0 vs. 38.0 months; HR: 0.42; 95% CI: 0.18–1.00; p = 0.051). In stage II-III patients who did not receive adjuvant chemotherapy, median RFS was prolonged in HER2-negative group in comparison to HER2-positive group (not reached vs. 12.0 months; HR: 0.17; 95% CI: 0.06-0.49; p = 0.001).

- ➔ RFS in Stage II or III patients who did not receive adjuvant chemotherapy: As shown in the figure below, there was no significant difference between the two groups (p=0.489).

➔ OS in Stage II or III patients who did not receive adjuvant chemotherapy: As shown in the figure below, there was no significant difference between the two groups (p=0.212).





#4 Table 1 should include the information about the number of patients who received adjuvant chemotherapy.

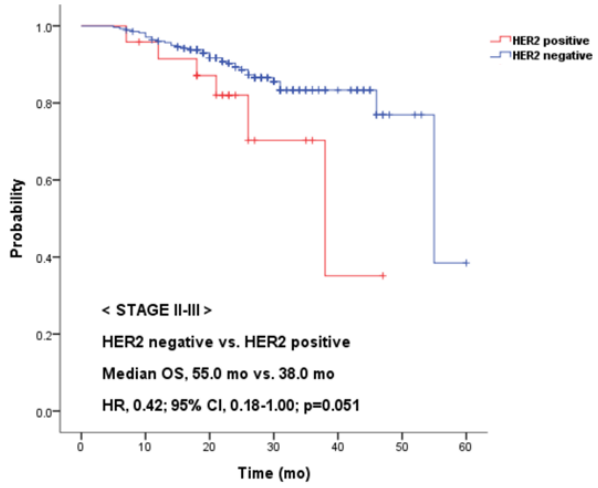
➔ We added the number of patients who received adjuvant chemotherapy in Table 1.

#5 Table 3 did not show how many factors were included for univariate and multivariate analysis. I think the adjuvant chemotherapy is one factor for the analysis.

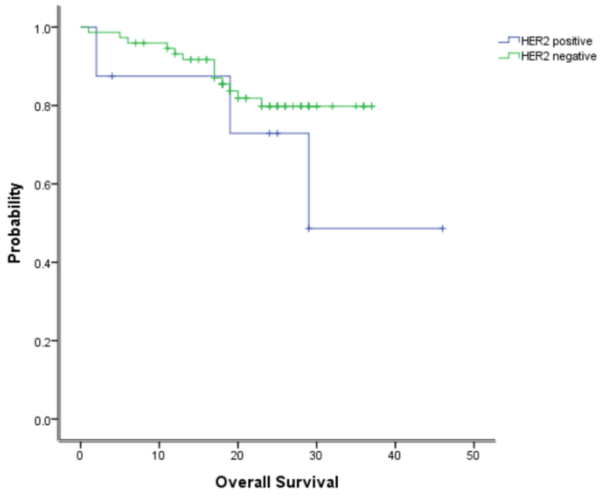
➔ We inserted an additional factor for the analysis in Table 3.

#6 Compared Fig.3 and Fig.4, OS in patients without overexpression of HER2 is longer in patients who did not receive the adjuvant chemotherapy than those received with adjuvant chemotherapy. What is the reason for this? Is selection bias such as that the patients who did not receive adjuvant chemotherapy were likely in Stage II?

➔ Thank you for pointing out this important issue. Median OS in patients without overexpression of HER2 was 55.0 months in patients who received with adjuvant chemotherapy. However, HER2 negative patients who did not receive adjuvant chemotherapy did not reach median OS. As shown in graphs below, the number of patients who did not receive adjuvant chemotherapy was too small. Also, longer follow-up duration is needed. To address your comment, patients who received adjuvant chemotherapy had more advanced N stage ($p=0.039$) than those who did not receive adjuvant chemotherapy. Therefore, in part, there was little difference between the two groups.

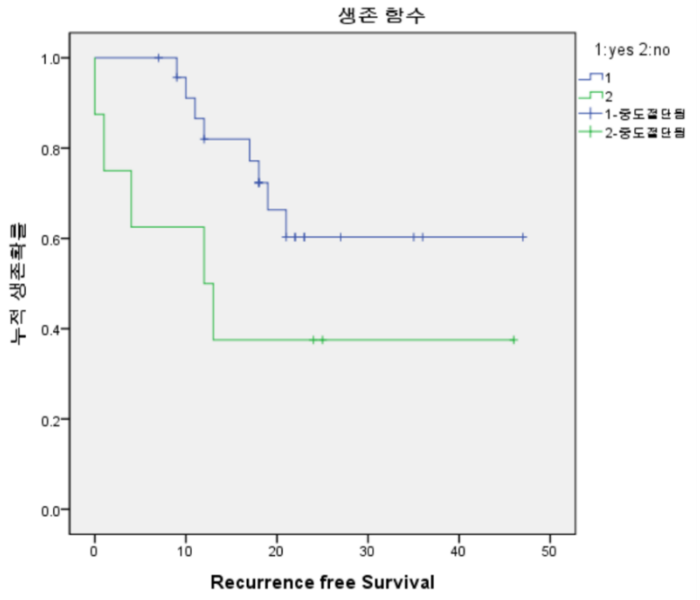


➔



#7 In addition, is the adjuvant chemotherapy effective for the patients with HER2 overexpressed gastric cancer?

➔ As shown in graphs below, for HER2 positive stages II-III of gastric cancer, median RFS was prolonged in patients who received adjuvant chemotherapy compared with those who did not receive adjuvant chemotherapy (not reached vs 12.0 months; p=0.090). Also, median OS was prolonged in patients who received adjuvant chemotherapy compared to those who did not; however, the difference was not statistically significant (38.0 months vs. 29.0 months; p = 0.669).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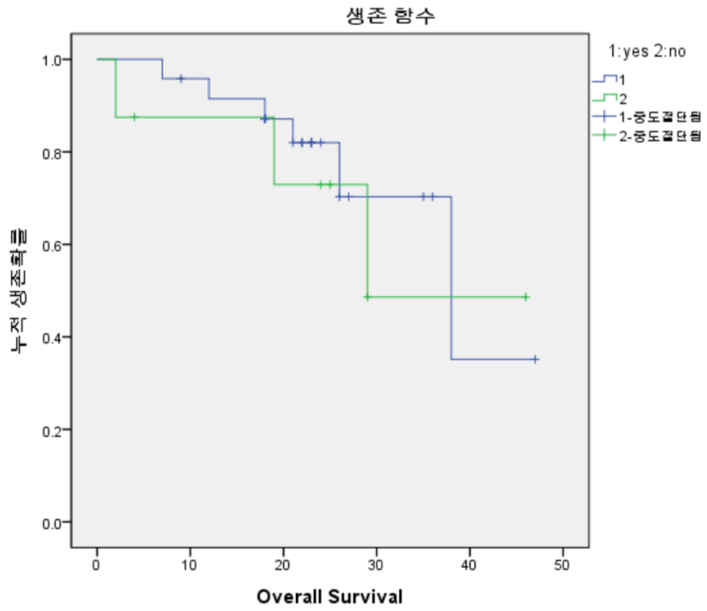
0.4
0.2
0.0
0
10
20
30
40
50
Recurrence free Survival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누적 생존확률
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0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Overall Survival