

Review

In the article: "Macroscopic appearance (Type IV and giant type III) is high risk for poor prognosis in pathological stage II/III advanced gastric cancer with postoperative adjuvant treatment." The authors present a study on the prognostic effect of macroscopic appearance in JGCA stages II and III in patients after R0 resection and adjuvant S1 chemotherapy and evaluate the potential value of this factor as a preoperative selection criterion for neoadjuvant treatment. Their results show that the macroscopic types giant III and IV have a significant negative prognostic effect on OS and RFS. The survivals in patients expressing these phenotypes are inferior to average risk patients, therefore the authors conclude that these patients would benefit from additional neoadjuvant treatment. Since the macroscopic appearance can be accessed preoperative, this could potentially serve as a selection criterion for neoadjuvant treatment.

The article has important merits and would be a valuable contribution to the journal, but there are some points that should be addressed before publication.

Than you for your positive comments. I revise our manuscript as you pointed out one by one.

Comment 1: Introduction: "... among which high risk patients with dismal prognosis was enriched in type IV and large type III gastric cancer. «

The sentence is difficult to understand, please rephrase.

Yes, I corrected it on page 3.

Comment 2: In the section "registration of patients" the authors mentioned that 26 D1 lymphadenectomies were performed. Since D1 lymphadenectomy is a major prognostic predictor, the authors should include the distribution of lymphadenectomy extent in the comparison between average and high risk patients to see whether s lesser extend of the lymphadenectomy could confound the OS and RFS.

Yes, I included the distribution of lymphadenectomy extent in Table 3.

Comment 3: Patients and methods, The 13th JGCA stage: For better comparison of the results and better understanding of the results for Western readers, it would be helpful to include the UICC TNM classification.

Yes, I included the UICC TNAM classification in Table 3.

Comment 4: Results, Multivariate Cox proportional hazards model for RFS identified macroscopic high risk as an independent prognostic factor in pathological stage II/III: "These significant prognostic factors for RFS

excluding TNM factor components were applied to the multivariate Cox proportional hazard model...”

The authors have identified the TNM stage as a significant predictor in the univariate analysis, but have excluded the TNM stage from the multivariate analysis. Please explain the decision to exclude the TNM stage from the multivariate analysis as it is known to be the most powerful predictor for RFS. Is it possible that there is a significant correlation between the macroscopic type and TNM stage that would confound the results in the multivariate analysis, if both factors were included?

I did not exclude the TNM stage, and I excluded each factor of T, N, M factor, because the 3 factors are confounding factor of TNM stage. I added this description on page 11, line 13-14.

Comment 5: Results, Multivariate Cox proportional hazards model for OS identified macroscopic high risk as an independent prognostic factor in pathological stage II/III: “These significant prognostic factors for OS excluding TNM factor components were applied to the multivariate Cox proportional hazard model...”

Please explain the decision to exclude the TNM stage from the multivariate analysis.

I did not exclude the TNM stage, and I excluded each factor of T, N, M factor, because the 3 factors are confounding factor of TNM stage. I added this description on page 11, line 13-14.

Comment 6: Results, Recurrent patterns of macroscopic high risk gastric cancer: “... EGFR, HER2, HER3, IGF1R and EphA2 was also included in Table 3...”

These results are depicted in Table 4. Please correct.

Thank you for your notice. I corrected it.

Comment 7: Results, Recurrent patterns of macroscopic high risk gastric cancer: “Among the 11 recurrent cases, 9 showed strong expression (2+/3+) of EGFR and 10 cases exhibited positive immunostaining (1+/2+) of HER3, which were both remnant independent prognostic factors in pathological stage II/III advanced gastric cancer.”

The high risk macroscopic type was identified as a risk factor for recurrence. These patients exhibited positive immunostaining for EGRF and HER3. Is there a correlation between expression of these markers and the high risk macroscopic type? Could the high risk macroscopic type serve as a surrogate marker for the expression of EGRF and HER3. Are there any implications for target treatment? Please discuss.

Yes, we previously reported HER3 is important as a prognostic factor in advanced gastric cancer. HER3 targeting is a promising strategy, so we are now testing in vitro now. I added it in the discussion on page 15 to 16.

Comment 8: Discussion: "... cancer with pathological stage II/III who underwent standard treatment."

The authors refer to S1 adjuvant treatment as standard treatment. The S1 adjuvant therapy is the standard treatment in Asiatic countries, whereas in the Western world other treatment options are reserved for gastric cancer patients. Please rephrase "standard treatment".

Standard treatment in Japan may be a right word.

Comment 9: Discussion: "... such potent chemotherapy may be a clue to regulate aggressive gastric cancer."

The sentence is difficult to understand, please rephrase.

Yes, I corrected it.

Comment 10: Discussion: "... that long-term survivors were enriched..."

The sentence is difficult to understand, please rephrase.

Yes, I corrected it.

Comment 11: Discussion: "...showed that 2-yaere..."

Please correct.

Year is the right word.

Comment 12: I suggest a proofreading of the English.

I asked a proofreading of the English.

Reviewer 2

Dear Editor, Yamashita et al presented a study title as "Macroscopic appearance (Type IV and giant Type III) is high risk for poor prognosis in pathological stage II/III advanced gastric cancer with postoperative adjuvant chemotherapy". The study have some new and interesting findings which I believe they add some contribution to the literature. Authors were well summarized results, they have novel findings and discussion was pretty good. I think this study can be published in the WJG. Thank you so much for your choice me as a reviewer.

Thank you for your kind comments.

Reviewer 3

This study aims to clarify the clinicopathological relevance of the macroscopic features of patients with advanced gastric cancer by analyzing the cumulative 5-year survival (OS) and cumulative 5-year relapse free survival of macroscopic high and average risk patients. Authors demonstrated that high risk gastric cancer patients have poorer prognosis than average risk gastric cancer. In the discussion part, the authors also described the different strategies and outcomes of perioperative chemotherapy between the Western and Eastern world and some other therapeutic strategies. The design of experiment is rigorous, the statistic method is reasonable and the language is very smooth, however, there still exists the following problems:

Thank you for your pertinent comments.

1) In the first part of the results, the reason why Pathological stage II/III cases did not include those with pathological stage II T1 gastric cancer was not explained.

In this study, we excluded T1 gastric cancer. We added the sentence on page 5.

2) Authors thought that this study was the first time to reveal the prognostic relevance of macroscopic high risk cancer. However, the application of these results is not novel. It has to be described why this method of judging prognosis is better or different from other methods like predicting by AJCC staging system or 13th JGCA staging system. What is the difference between your clinicopathological relevance of the macroscopic features and TNM stage?

I deleted the incorrect word.

3) This study was a single-center study, and the follow-up period was short. The sample size was small. If this study enrolled a larger sample size or had a longer follow-up period, the results would be more meaningful. For example, when authors analyzed the recurrent patterns of macroscopic high risk gastric cancer,

the whole conclusion was based on small numbers (11 cases) and the findings could easily be spurious.

I included limitation before conclusion as you pointed out.

4) The quotations content is not closely related to the topic of this paper. Authors discussed too much about the efficacy of different perioperative treatment strategies instead of the prognostic relevance of macroscopic features of gastric cancer. Please add the related content.

I added the related content on page 15 to 16.

5) The conclusion is overstated. For example, this study only collected patients who underwent curative surgery plus adjuvant S1 chemotherapy. But authors didn't mention if these results can be seen from other patients with advanced gastric cancer.

I should have mentioned if these results can be seen from other patients with advanced gastric cancer. I added it as limitations before conclusion.

6) The epidemiology and the data of gastric cancer-related death in 2012 might be out of date and should be updated.

I updated it as a new reference.

7) In your article, "All histologic and clinicopathological factors were assessed independently and blindly by histopathologists" is not rigorous enough. The number of histopathologists should be clarified and the experience of histopathologists should be balanced.

Histopathologists number was included on page 7.

8) In the "Statistical Analysis" part, RFS was measured from the date of surgery to the date of recurrence or the last follow-up in your study. However, the way and internal to evaluate recurrence was not clearly demonstrated.

The way and internal to evaluate recurrence was added on page 8.

Reviewer 4

The article „Macroscopic appearance (Type IV and giant type III) is high risk for poor prognosis in pathological stage II/III advanced gastric cancer with postoperative adjuvant treatment“ presents a new approach (for eastern world)

for patients with macroscopic appearance stages II and III after R0 resections combined with S1 chemotherapy. The authors showed that patients with this stage of gastric cancer would benefit from additional neoadjuvant chemotherapy. The article have important and interesting findings and I believe they add some contributions to the literature about gastric cancers especially in eastern countries. Despite this is a single-center study and the sample size is small, By me the article can be publish in the World Journal of Gastroenterology. There are some points that should be addressed before publication.

Thank you for you positive comments.

1. There are noticeable minor language mistakes. I'm suggesting to perform a proofreading of the English.

I asked proofreading for English native speaker.

2. Authors used only the 13th JGCA classification. In my opinion for better understanding of the results/conclusions for Western readers, it would be helpful to use the TNM classification.

I use the UICC TNM classification, too.

3. In the parts of results / tables appears term young patient with stomach cancer - what is the criterion of age, and why?

I explained the criterion of age as reference of 11 on page 5.