Comments to reviewers

Reviewer #1

This manuscript in present form does not have much clinical relevance. It's value for patient benefit would be raised by addressing below comments. Specific comments.

Answer: Thank you for your favorable comments. According to your suggestion, we revised and deepened our manuscript.

1. Reference 12 is not a good reference to support assertion. This is a phase II trial of intraperiotoneal therapy which treats transcoelomic spread and not relevant in this situation. Contrary to this there is level 1 evidence for the benefit of adjuvant therapy in both Western and Asian populations with gastric cancer. There are large well conducted phase III trials to support this: MAGIC, CLASSIC, ACTG-GC, The GASTRIC metanalysis further supports the benefit of adjuvant systemic therapy in gastric cancer as a standard of care.

   Answer: This review is not specialized in adjuvant chemotherapy. We showed the possibility that treatment for peritoneal metastasis should be developed. Phase III trial of intraperitoneal therapy using paclitaxel is ongoing. While this reference is Phase II trial, the efficacy is phenomenal, 1-year survival rate is 78% and response rate is 56%. Then we cited this article.
2. INT0116 demonstrates benefit of chemoradiotherapy as a adjuvant strategy.

   Answer: This review is not specialized in adjuvant chemotherapy.
3. The focus of this review should be to evaluate potential targets that can be drugable to improve on the present treatments which are considered to be best practice and standard of care.

   Answer: This review aims to summarize the molecules reportedly contributing to hematogenous metastasis from GC and to become the groundwork for the further development of novel biomarkers and molecular targets.
4. Matrix metalloproteinases have already been targeted in clinical trials. Marimastat trialed in the 1990's. Gilead GS5745 in present clinical testing in advanced gastric cancer.

   Answer: We did not know that anti-MMP9 antibody was in present clinical phase III trial. Thank you for telling us. We judged not to add the clinical trial as a reference because the result of the clinical trial has not been yet out and published.
5. Exosomes to deliver miRNA 214 to reverse cisplatin in tumour resistance.

   Answer: Wang X et al. reported that exosomal-anti-miR214 could reverse the resistance to DDP in gastric cancer (Mol Ther. 2018 Mar 7;26(3):774-783. Epub 2018 Jan 8). In this section, we focused on premetastatic niche specific for hematogenous metastasis from gastric cancer. We would like to entrust the mechanisms of systemic resistance for

chemotherapy to another review.

6. NFKB as target. Justification: Chemotherapy can elicit cellular stress that confers chemoresistance through NFKB.
   Answer: According your useful suggestion, we added some sentences in NFKB section.
7. VEGF as target. Bevacizumab (AVAGAST study) and ramucirumab (RAINBOW and REGARD trials) proven in clinical management.
   Answer: According your suggestion, we added a sentences in VEGF-D section regarding with anti-VEGFR monoclonal antibodies.
8. IL6 antibodies available.
   Answer: Anti-IL-6 monoclonal antibody, siltuximab was evaluated its efficacy and safety in phase I/II trial. Siltuximab was mainly used in hematopoietic tumors, and in solid tumors with very small number of patients. These trials did not include patients with gastric cancer. Then we did not mention anti-IL-6 antibody in this review.
9. Her2 targeting used routinely in metastatic gastric cancer with Her2 overexpression. ToGA trial of trastuzumab. Trial of lapatinib.
   Answer: In HER2 section, we referred to the anti-HER2 monoclonal antibody.
10. Listing HIF targeting drugs available and where they are in clinical testing.
    Answer: According your suggestion, we added a sentences in HIF-1α section regarding with HIF-1α inhibitors.

Reviewer #2

Shimizu et al. reviewed the molecules reportedly contributing to hematogenous metastasis from gastric cancer and to become the groundwork for the further development of novel biomarkers and molecular targets. Comments This is an interesting review article. This manuscript is well-written. The authors provided the novel information for the molecular landscape specific for hematogenous metastasis from gastric cancer. The reviewer has no further comments and this review article can be accepted to publish.

Answer: We thank the favorable comments. We were encouraged to resubmit our manuscript to *World Journal of Gastrointestinal Oncology*.

Reviewer #3

This work by Drs. Shimizu et al., have summarized molecules reportedly contributing to hematogenous metastasis from gastric cancer (GC), the authors intend to establish the landscape of molecules that specifically participate in metastasis in distinct secondary organs in GC, and hope this will lead to the development of novel biomarkers for patient stratification. Numerous published works have indicated various molecules that are involved in the processes of

metastasis, this work focus on hematogeneous metastasis markers as potential marker in this process. The work is therefore interesting, novel with merit. The manuscript appears well organized and written, but also appears missing in-depth analysis of the selected molecules and inner link between the metastasis and mechanisms, of which important aspects are roles of epigenetics, stem cell, E-cadherin etc. The work may require more in-depth revision with supporting data to strengthen the claim and point out directions for future investigation to guide readers. Authors are encouraged to revise and add more input to make the manuscript more attractive theoretically.

Answer: We thank the reviewer's useful comments. We revised our manuscript according the comments and added clinical relevance including clinical trials and molecular targeted agents already used in clinical management in several genes.