



April 29, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **10282**-review.doc).

Title: Successful esophagectomy in a patient with combined esophageal cancer and hemophilia B

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Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) *"The importance of the research and the significance of the research contents; The authors of this article have been evaluated the case report which describe the perioperative management for reducing the risk for postoperative hemorrhage in hemophilia patients with esophageal cancer that need esophagectomy with esophagogastrotomy. Although recent reports on the surgical treatment for patients with hemophilia have been published, no detailed case reports are available on major operations such as esophagectomy. The importance and significant of the research contents is not high, because this combination of conditions (hemophilia and esophageal cancer) is rare."* **(Reviewed by 02861131)**

Answer: The incidence of complications such as hemorrhage during surgery for esophageal cancer is high, especially in patients with preoperative coagulopathy. Based on our findings from this case report, we believe that in patients with hemophilia, surgery can be safely performed with appropriate perioperative management.

(2) *"Case report is well organized and analyses of modality to select the appropriate surgical approach are providing. Unfortunately, the authors don't present valuable conclusion."* **(Reviewed by 02861131)**

Answer: Thanks you for your comment. The incidence of complications such as hemorrhage during surgery for esophageal cancer is high, despite the use of minimally invasive surgery. Without appropriate intervention, the risk for major intraoperative and postoperative hemorrhage is considerably high in patients with esophageal cancer and hemophilia. In this case report, we considered that surgery can be safely performed in patients with hemophilia with appropriate perioperative management.

(3) *"The case report is important from the hematologist and surgical point of view. However few points need to be revised: 1) Retrospective anamnesis is missing. Screening for inhibitor factors prior and during surgery has to done and provided. 2) Picture of the surgical technique has to be added 3) English Language revision needed."* **(Reviewed by 02861170)**

Answer: 1) As described in the Case Report, the retrospective anamnesis only included the surgical

history of the removal of an abdominal hematoma 10 years prior. The patient denied other medical histories. The patient did not know that he had hemophilia prior to admission. After diagnosis of hemophilia B, owing to the cost and unstable sourcing process of coagulation factor IX concentrates, we administered a perioperative intravenous infusion of the prothrombin complex concentrate, which is easy to source, to replenish coagulation factor IX. Therefore, we did not screen for inhibitor factors before and during surgery. 2) As suggested by the reviewer, we have added the related figures. However, if the editor thinks that those figures are unnecessary, we agree to delete them. 3) We have corrected the grammatical errors in our manuscript according to the reviewer's suggestion, and the revised manuscript has been checked again by a native English speaker experienced in editing medical papers.

(5) *"This case report is important for surgeon and internist or hematologist. there are some advise: 1). the word "combined" in the titleCombined Esophageal Cancer and Hemophilia B was not appropriate in this term. I think combined must be changed to co-morbid. 2). how to prepare hemophilia B patient who undergo surgery of esophageal cancer due to occurring of severe hemorrhagic during and after surgery is a common procedure in hematology disorder patients.Ivor Lewis esophagectomy was a common minimally invasive esophagectomy technique. If you mentioned to the "hybrid minimally invasive Ivor-Lewis esophagectomy", you must explain the advantage of hybrid minimally invasive Ivor-Lewis esophagectomy compared to minimally invasive Ivor-Lewis esophagectomy. 3) very interesting thing, if you insert the picture of the surgery technique of the patient to the manuscript. "* (Reviewed by 02861175)

Answer: 1) We have corrected the grammatical errors in our manuscript according to the reviewer's suggestion. 2) Just as described in the Discussion, we used hybrid Ivor-Lewis esophagectomy to complete gastric mobilization and jejunostomy in the abdomen under laparoscopy in this patient. In the thorax, we performed esophageal mobilization and resection, mediastinal lymph node dissection, gastric conduit construction, and esophagogastrostomy via a right lateral thoracotomy under direct vision, which required lesser time than thoracoscopy. 3) As suggested by the reviewer, we have added the related figures.

(6) *"The manuscript needs thorough English Language revision. The utility of the phrase "No significant abnormalities were found on physical examination, and no superficial bleeding or bruising was found on the skin" is not clear; it should be removed altogether, or rather a more proper statement providing an assessment of his hematological state should be made. It is not clear if bleeding time is performed in all patients routinely. Although it has been reported, the diagnosis of hemophilia in this case was made at a considerable age (45 years). In this sense, a parragraph explaining the retrospective anamnesis should be added. It is not clear if screening for inhibitor factors was performed prior to the scheduled surgery. According to present guidelines, measurement of serial factor levels during the surgical procedure must be carried out, and in the present report this is not even mentioned. It is clear that direct supplementation of the deficient coagulation factor is the most adequate therapeutic and preventive measure; however, the authors explain that due to its cost, this strategy was not followed. If such major surgery is to be performed, the use of this factor is probably justified. Anyhow, a word of caution on thrombotic adverse events with the use of prothrombin complex concentrate is warranted. The manuscript could probably benefit from an illustration of the surgical technique employed."* (Reviewed by 02861195)

Answer: 1) Thank you for your comment. We have corrected the grammatical errors in our manuscript according to the reviewer's suggestion. 2) As described in the Case Report, the retrospective anamnesis only included the surgical history of the removal of an abdominal hematoma 10 years prior. The patient denied other medical histories. 3) Indeed, direct supplementation of the deficient coagulation IX factor

is the most adequate therapeutic measure. However, due to the cost and unstable sourcing process of coagulation factor IX concentrates, we administered a perioperative intravenous infusion of the prothrombin complex concentrate, which is easy to source, to replenish coagulation factor IX. According to the World Federation of Hemophilia guideline on the management of hemophilia, intravenous infusion of prothrombin complex concentrate is a safe and simple approach. 4) We have added the related figures suggested by the reviewer.

(7) "Good job...There is two important point, I think. 1)Some patients may not know that they have hemophilia prior to operation. Therefore, further tests and screening for hemophilia are essential for patients with preoperative coagulopathy to control the risk for intraoperative and postoperative hemorrhage, 2)Perioperative intravenous infusion of the prothrombin complex concentrate that be used to replenish coagulation factor IX is a simple method, and the medication is easy to source, hence avoiding the which mentioned some important problems." **(Reviewed by 02861252)**

Answer: Thank you for your comment.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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