

Dear Editor:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate you and reviewers very much for your positive and valuable comments and suggestions on our manuscript.

Title: How to examine the anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? methylene blue testing prevents technical defect-related anastomotic leaks

ID: 73067

Based on these comments and suggestions, we have made careful modifications on the original manuscript, all changes made to the text are in red color. Please see our point-to-point responses to all your comments below. In order to make our manuscript more idiomatical and meet the publishing requirement of the World Journal of Gastrointestinal Surgery, we polish our manuscript by AiMi Editor before we submitted our manuscript.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Yours sincerely,

Xiaojun Li

Answers to reviewers:

Reviewer 1

Summary: This is a manuscript that aims to investigate whether intraoperative methylene blue administration is a suitable test to evaluate the anastomotic integrity of esophagojejunostomy or gastrojejunostomy after totally laparoscopic radical gastrectomy, and to investigate what the effect of intraoperative methylene blue testing (IMBT) is on the incidence of postoperative anastomotic leakage (AL). In addition, they aim to identify risk factors for positive IMBT and for developing AL. To achieve this, a retrospective study was

conducted that included patients treated between January 2017 and December 2019. A total of 513 patients underwent totally laparoscopic radical gastrectomy because of gastric cancer or adenocarcinoma of the gastroesophageal junction.

From these patients, 211 received IMBT and 302 did not receive IMBT. Seven patients had a positive IMBT, which required additional sutures. None of these patients developed AL. Fifteen patients did develop AL, two in the IMBT group and 13 in the control group. Risk factors for a positive intraoperative IMBT after univariate analysis were surgeons who performed <50 totally laparoscopic radical gastrectomies, operation time >4 hours, neoadjuvant chemotherapy and BMI >25 kg/m². After multivariate analysis, BMI >25 kg/m², operation time >4 hours and insufficient surgical experience (<50 totally laparoscopic radical gastrectomies) were identified as independent risk factors for positive intraoperative IMBT.

Patients with preoperative BMI >25kg/m², who experienced preoperative complications, received neoadjuvant chemotherapy and who underwent a totally laparoscopic total gastrectomy had a higher risk of developing AL. After multivariate analysis only preoperative complications, totally laparoscopic total gastrectomy and neoadjuvant chemotherapy were independent risk factors for AL.

Although the goal and the importance of this study are clear, there are some concerns and questions which I will explain below.

General

The verb tenses used in the manuscript should be thoroughly revised. For example, in the introduction the past tense is often used. In the method sections, the verb tenses used change throughout the paragraph.

Response: We greatly appreciate your time and expertise in reviewing our manuscript. We have carefully revised the verb tenses according to your constructive comments, which significantly improve our manuscript. This manuscript is polished by a native English editor for grammatical errors and non-standard English expression. Thanks again for your positive enthusiasm for our work.

Abstract

1.Aim: consider to add in what type of operations IMBT is investigated.

Response: Thanks for your kind advice. As suggested, we added the type of operation as shown below;

“To explore the effects of IMBT on the incidence of postoperative anastomotic leaks (PALs) and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.”

2.Methods: Please explain what the experimental group and control group are.

Response: Thanks for the comment, the definitions of experimental group and control group have been added to the revised version of the article as shown below;

“From January 2017 to December 2019, patients who underwent totally laparoscopic radical gastrectomy in the Shaanxi Provincial People's Hospital are retrospectively analyzed and grouped according to whether an IMBT needs to be performed or not. The patients were divided into the IMBT group and the control group.”

3.Results: important results such as total included patients, the amount of patients in IMBT group and control group are not described. Besides that, the order in which the results are showed is illogical.

“There were no PAL when an intraoperative leak led to concomitant intraoperative repair. Moreover, 15 patients (2.9%) developed PALs, with a higher incidence in the control group than in the experiment group (4.3% vs. 0.9%, P=0.026).” Please rewrite this sentences, unclrear.

Response: Adhering to these important suggestions by the reviewer, we have described these important results in the revised manuscript. The order of the results is rearranged according to logic. We rewrite these sentences. The results are shown as follow:

“This study consist of 513 patients, 211 in the IMBT group and 302 in the control group. A positive IMBT is shown in 7 patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement, a multivariate analysis showed that risk factors for predicting a positive IMBT are body mass index (BMI) >25kg/m² (HR=8.357, P=0.009), operation time >4h (HR=55.881, P=0.002), and insufficient surgical experience (HR=15.286,

P=0.010). Moreover, 15 patients (2.9%) developed PALs in both the IMBT group and the control group, and the rates of PALs are significantly lower in the IMBT group than in the control group (2 of 211 patients (0.9%) vs. 13 of 302 patients (4.3%), P = 0.0026). Further analysis demonstrated that preoperative complications (HR=13.128, P=0.017), totally laparoscopic total gastrectomy (HR=9.075, P=0.043), and neoadjuvant chemotherapy (HR=7.150, P=0.008) are independent risk factors for PALs.”

Introduction

1. Please rewrite the sentence: ‘‘However during laparoscopic radical gastrectomy, there was no study to date that assesses anastomotic integrity after systematically searching the literature’’. I understand what you want to say, but it is a strange sentence.

Response: Many thanks for your advice. The sentences have been modified as follows.

‘‘However, to the best of our knowledge, no study has assessed the integrity of anastomosis during totally laparoscopic radical gastrectomy.’’

Methods

Patients

1. Consider to rename the two groups. experimental and control maintain the appearance that an active ‘‘new’’ intervention has taken place. However, it is a retrospective study where apparently IMBT was already used in daily practice.

Response: The reviewer is exactly right, we rename the two groups. IMBT group and control group would be better.

2. Please replace the last part of this paragraph ‘‘In our department .. Reflux esophagitis’’ to the next paragraph ‘Surgical methods and postoperative management’.

Response: Thanks for your professional advice. As your suggested, we have replaced the last part of this paragraph ‘‘In our department.. Reflux esophagitis’’ to the next paragraph ‘Surgical methods and postoperative management.

Methylene Blue Testing Technique

1. I do not understand why some patients received IMBT and the others didn’t. Was it the surgeons decision? If yes, was it because the surgeon did not trust the created anastomosis (less experienced surgeon)? Were there signs to doubt the anastomotic integrity (difficult/long operation)? Or was IMBT introduced at one point somewhere between 2017-2019 and the first 302 patients in the ‘‘control’’ group just did not receive IMBT because it was introduced after they were operated? (bias because of learning curve)

Response: Thank you for your comments. The data of this article were obtained from Shaanxi Provincial People's Hospital between January 2017 and December 2019. In our department, totally laparoscopic radical gastrectomy has been performed since January 2017. Some surgeons think IMBT is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy, while others are skeptical regarding the effects of IMBT. Thus, some patients received IMBT and the others didn’t. This is also the purpose of our manuscript to tell everyone that IMBT can be used to check the integrity of anastomosis during totally laparoscopic radical gastrectomy. We plan to perform a RCT to further confirm the effects of IMBT. Once again, thank you for your comments, we have done the following revisions and additions in our manuscript:

‘‘In our department, some surgeons think IMBT is useful, while others are skeptical regarding its effects. Thus, two groups are formed: an IMBT group and a control group.’’

2.Please adjust the used verb tense. It changes throughout the whole paragraph.

Response: We thank the reviewer for this helpful suggestion and have revised the verb tense. This manuscript has been polished by an English language editing company.

3. What do you mean with “anal side of the anastomosis”? The distal part? Please change this description.

Response: Many thanks for your comments. Yes, we mean the distal part. We have changed this description as you suggested.

Definition

1. What is the used definition of anemia? Hemoglobin level of < ..?

Response: Thank you for your comments. In the revised manuscript, we added the definition of anemia and references:

“The World Health Organization's definition of anemia is used to define anemia, patients with Hb concentration of <12 g/dL in women and <13 g/dL in men is defined as anemia^[1]. ”

[1]. World Health Organization Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. [(accessed on 21 June 2021)]; Available online: <https://www.who.int/vmnis/indicators/haemoglobin/en/>

2. Please explain what the used definition of “malnutrition” is or where it was based on.

Response: Thank you for your advice. We added the definition of “malnutrition” and references in the manuscript:

“Malnutrition is defined by the European Society of Clinical Nutrition and Metabolism (ESPEN) criteria^[2], which suggests two methods used to diagnose malnutrition. Method one: Body mass index (BMI) <18.5 kg/m². Method two: Unintentional weight loss combined with a low age-related BMI (<20 kg/m² in <70 years or <22 kg/m² in ≥70 years) or low fat-free mass index (FFMI) (<17 kg/m² in men and <15 kg/m² in women). ”

[2] Cederholm T., Bosaeus I., Barazzoni R., Bauer J., Van Gossum A., Klek S., Muscaritoli M., Nyulasi I., Ockenga J., Schneider S.M., et al. Diagnostic criteria for malnutrition—An ESPEN Consensus Statement. *Clin. Nutr.* 2015;34:335–340. doi: 10.1016/j.clnu.2015.03.001.

Statistical analysis

1. Please check the word "analysis", sometimes the singular word and sometimes the plural word is used. Also change the corresponding verbs.

Response: We thank the Reviewer for his/her comments and have addressed this question in our manuscript.

Results

Comparison of the incidence of PAL

1. Please describe the number of patients that developed AL in the group that received IMBT and the number of patients in the group that didn't receive IMBT.

Response: Thanks for your professional advice. As you suggested, we describe the number of patients in the IMBT group and control group as follows:

“PAL occurred in 15(2.9%) patients, including 2 in the IMBT group and 13 in the control group. The rate of PALs was significantly lower in the IMBT group than in the control group (2 of 211 patients (0.9%) vs. 13 of 302 patients (4.3%), $P = 0.0026$).”

The risk factors analysis of PAL

1. Please add to the risk factor “totally laparoscopic gastrectomy” if it is about the total gastrectomy or the distal gastrectomy.

Response: I sincerely apologize for this mistake. The correct expression is “totally laparoscopic total gastrectomy”. We have revised the expression in manuscript.

Reviewer 2

The overall quality of the manuscript is good, and the article should be accepted for publishing with high priority.

Response: Thanks for the reviewer's positive comments on our manuscript.

2 Editorial Office's comments

1) Science Editor: I would like to congratulate the authors for the enthusiasm invested in this study. However, the manuscript does not reach the level of quality required for publication as original article without major revision based on the reviewers' comments.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Response: Many thanks to the editor for the editor's recognition of our work. We have carefully revised the manuscript according to reviewers' comments. This manuscript has been polished by a native English editor for grammatical errors and non-standard English expression. Once again, thank you to the Editor and Reviewers for their thoughtful, diligent, and respectful critique of our paper.

2) Editorial Office Director: I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: Thank editors for your valuable comments. It's my honor to publish this manuscript in the World Journal of Gastrointestinal Surgery. As your suggested, we have the uniform presentation in figures and provide decomposable Figures in a single PowerPoint file. Standard three-line tables are used to meet the requirements of the World Journal of Gastrointestinal Surgery. Again, we thank the editor for this valuable opportunity.

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Gastrointestinal Surgery. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological

changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: Thank editors for your valuable comments. It’s my honor to publish this manuscript in the World Journal of Gastrointestinal Surgery. As your suggested, we have the uniform presentation in figures and provide decomposable Figures in a single PowerPoint file. Standard three-line tables are used to meet the requirements of the World Journal of Gastrointestinal Surgery. Again, we thank the editor for this valuable opportunity.