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To:
Editors-in-Chief
of the
World Journal of Clinical Cases

30.03.2022

Subject: Submission of Revised Manuscript NO: 74360

Dear Editors,

please find attached our revised case report entitled "***Beware of gastric tube in esophagectomy after gastric radiotherapy – a case report with review of the literature***", which we have submitted to **World Journal of Clinical Cases** as offered by the peer-reviewers and editors of **World Journal of Gastroenterology**, to which we had submitted the manuscript initially. The reviewer's comments can be found in the rebuttal letter added to this writing.

We confirm that all authors viewed and approved and are fully conversant with the contents of the final revised version of this manuscript and have disclosed any aspects potentially conceived as a conflict of interest, disclosing ownership interests, patents and employment. We hereby confirm that the submitted manuscript has not been submitted to or is accepted for publication or already published in any other scientific journal.

We hope that you will consider our revised work for publication and we thank you very much for your support and the possibility to submit our case report to **World Journal of Clinical Cases** today.

Yours sincerely,
on behalf of all co-authors

Can Yurttas, MD

Karolin Thiel, MD

Reviewer #1: The present case report described a patient with previous gastric MALT lymphoma treated with sequential chemotherapy and radiotherapy; seven years later, the patient demonstrated gastric tube necrosis with anastomotic leak following esophagogastrostomy and was healed six months later with colonic interposition. The authors concluded that esophagogastrostomy should be avoided for patients with a long interval between gastric radiotherapy and esophageal surgery. The present research showed low-grade of evidence for this issue as a case report and several issues should be further clarified, as detailed below:

Major points:

1. preoperative radiotherapy does cause extra influence on anastomotic healing as evidenced by some reports (PMID: 24736077), and long intervals may further aggravate this issue as the authors suggested. However, anastomotic leak differs from tissue necrosis ! tissue necrosis is usually caused by inappropriate handling of supplying vessels leading to acute or chronic ischemia and subsequent necrosis. For this patient, the authors should specify the detailed surgical procedure, particularly the steps for perigastric vessel ligations, or provide intraoperative images if possible, such that an intraoperative mistake could be ruled out.

We would like to thank the reviewer for the remarks and the recommended reference. Although findings from the CROSS trial showed no increased risk of anastomotic leakage following neoadjuvant radiochemotherapy and esophagectomy ^[1], a retrospective analysis of Juloori et al indicates that preoperative radiochemotherapy with in-field anastomosis-creation increases the risk for leakage. We therefore added the mentioned reference with the following sentence to the discussion section: "In particular, no increase in anastomotic leakage was reported in the CROSS trial ^[1], whereas in-field creation of anastomosis following neoadjuvant radiochemotherapy and esophagectomy was identified as a risk factor for anastomotic leakage in a retrospective analysis of 285 patients treated for esophageal cancer ^[2]."

Unfortunately, we cannot provide images of the intraoperative situs and especially the perigastric vessel supply. However, esophagectomy for esophageal cancer with or without neoadjuvant treatment is a common procedure at our high-volume center with annually 40 – 50 cases of esophagectomy and 30 – 50 cases of gastrectomy and low overall complication rate so that we can rule out technical mistakes. In our long-term experience, we never observed a comparable case of complete gastric tube necrosis which makes technical flaws unlikely in our view. Moreover, the report of the pathologist does not describe any abnormalities of supplying vessels.

We further specified the surgical procedure in the "Material and methods section".

"Surgery was performed in a minimally invasive technique of Ivor Lewis esophagectomy. Access to the abdominal cavity and capnoperitoneum was established with the help of a Veress needle. An optic trocar was introduced under vision with a 30° camera (STORZ). The abdominal cavity was inspected to rule out injuries during access and also peritoneal or hepatic metastases. Then, gastric mobilization was performed with an electro-surgical vessel sealer, left gastric artery was clipped whereas the right gastric artery as well as the right gastroepiploic arcade were preserved. Complete D2-lymphadenectomy was performed followed by stapled gastric tube formation of approximately 5 cm in diameter. Esophagectomy including mediastinal lymphadenectomy was operated thoracoscopically with four right-sided intercostal trocars. The resection was completed with formation of a stapled circular end-to-side-esophagogastrostomy.

2. the patient took regular metformin and sitagliptin. Did he have type 2 diabetes? Type 2 diabetes per se is a risk factor for anastomotic leak. This issue should be clarified.

Thank you very much for the note. We added the following sentence to the "history of past illness" section: "The patient had a history of herniated vertebral disc, struma nodosa, chronic-venous insufficiency and endoscopic resection of a low-grade adenoma of the sigmoid colon and regularly took metformin, thyroxine and sitagliptin for type 2 diabetes mellitus and hypothyroidism respectively."

Reviewer #2: In this case report, the authors present an interesting and unique case of minimally invasive esophageal resection with esophagogastrostomy followed by gastric tube necrosis with anastomotic leakage and necessity of cervical salivary fistula.

I have few minor revisions :

- The title is informative.
- The abstract should be more informative: I would just add more information in the "Background part".

We have extended the "Background part" in the abstract to make it more informative: "Gastric tube formation and pull-up is the most common technique of reconstruction following esophagectomy for esophageal cancer. If previous treatment with radiotherapy for gastric MALT-lymphoma restricts suitability of the stomach for anastomosis to the esophagus is unknown."

- Page (P) 4 Line (L) 70 "tumor was in an early stage ": the TNM should be added.

The clinical TNM-classification has been added to the abstract "uT1 (sm2) uN+ cM0 according to TNM-classification"

- P4 L 75-76 "This case report gives reason.....I between gastric radiotherapy and surgery". This sentence should be changed. This assumption can't be supported just by a case report. I would change it into: "This case report may represent the start for further investigation to know if it is reasonable to refrain from esophagogastrostomy in patients with a long interval between gastric radiotherapy and surgery"

We totally agree with the reviewer's assessment that this case reports does not allow for conclusions but should rather be regarded as an impulse to do further investigations on this subject so that we appreciate the suggestion and replaced our sentence by the reviewer's.

- The Core tip is informative:
- P4 L 85 : "tumor recurrence at date of publication". "till" has been replaced by "at"
- The length of follow up in years and months should be added.

Follow-up has been added to the core tip: "The patient fully recovered with unlimited capability of oral intake and remains free of tumor recurrence at date of publication and follow-up of 16 months."

- The main text is well written and clear, I have few comments: P 6 L 120-121 and regularly took metformin, thyroxine and sitagliptin: from these medications, it looks like the patient is diabetic and might have hypothyroidism. If it is true this should be added in the text.
- Thank you very much for the note. We added the following sentence to the "history of past illness" section: "The patient had a history of herniated vertebral disc, struma nodosa, chronic-venous insufficiency and endoscopic resection of a low-grade adenoma of the sigmoid colon and regularly took metformin, thyroxine and sitagliptin for type 2 diabetes mellitus and hypothyroidism respectively."

- Other important information is missing: the BMI, wheater he smokes or not, his alcohol intake, his diet, if he has gastroesophageal reflux. Those are all risk factors for esophageal cancer.

This is absolutely correct so that we added the BMI and information about smoking, alcohol intake, diet and gastroesophageal reflux: "Due to asymptomatic **gastro-esophageal reflux disease** with Long Segment Barrett's esophagus C9M13 according to Prague Classification, a 64 years old patient underwent repetitive esophagogastroduodenoscopy. In 2020, biopsy of the distal esophagus 34 cm from row of teeth revealed invasive moderately differentiated (G2) adenocarcinoma. Moreover, erythema and atrophy of the gastric mucosa was detected. However, the patient had no disease-specific complaints when he first presented to our department. **Oral intake of standard western-diet was unrestricted and body weight was constant at a BMI of 29.1 kg/m². The patient had skipped drinking and smoking after intake of 60 pack-years.**"

- Conclusions are informative, however, P9 L 220-223 should be changed. We, therefore, recommend that stomachs pretreated with radiotherapy should not be knowingly used for reconstruction in esophagectomy. We provide little evidence from a single patient only and without proven causality". A recommendation can't be made based on a single case report. The authors should make clear that this represents a pivotal case report but further studies are necessary to have evidence-based proves.

Drawing conclusions from a single patient is truly illegitimate. We therefore changed our concluding sentence as follows: "**Although this case report provides little evidence from a single patient only without proven causality, further investigations as to whether stomachs pretreated by radiotherapy in general should not be utilized for reconstruction in esophagectomy are required.**"

- Minor English revisions are necessary.

We are somewhat astonished about the reviewer's concern as the whole manuscript has been edited by a certified English native-speaking professional translator and interpreter (Mrs. Mary Heany MARGREITER, see also <http://margreiter-translation.com/>).

However, the complete manuscript has been proofread again to check for mistakes and corrections were made if indicated.

2 Editorial Office's comments

1) Science Editor: The manuscript mainly focus on the gastric tube in esophagectomy after gastric radiotherapy, and the manuscript fall within the scope of the journal, but it need major revisions according to reviewers' comment before accept.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade D (Fair)

We are somewhat astonished about the editor's concern as the whole manuscript has been edited by a certified English native-speaking professional translator and interpreter (Mrs. Mary Heany MARGREITER, see also <http://margreiter-translation.com/>).

However, the complete manuscript has been proofread again to check for mistakes and corrections were made if indicated.

2) Editorial Office Director: I recommend the manuscript to be published in the World Journal of Clinical Cases.

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Clinical Cases.

References

- 1 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. *The New England journal of medicine* 2012; **366**(22): 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa1112088]
- 2 Juloori A, Tucker SL, Komaki R, Liao Z, Correa AM, Swisher SG, Hofstetter WL, Lin SH. Influence of preoperative radiation field on postoperative leak rates in esophageal cancer patients after trimodality therapy. *J Thorac Oncol* 2014; **9**(4): 534-540 [PMID: 24736077 PMCID: PMC3989552 DOI: 10.1097/jto.000000000000100]