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Associate Editor

World Journal of Clinical Cases

Manuscript for Submission: “Local advanced rectal cancer perforation in the midst of preoperative chemoradiotherapy: A case report and literature review,” by Takase *et al.*

ESPS Manuscript NO: 29691

Dear Editor,

Thank you very much for reviewing our manuscript by Takase *et al.* (ESPS Manuscript NO: 29691). We hope that you find our manuscript suitable for publication in *World Journal of Clinical Cases (WJCC)* after revision along the reviewers' comments.

According to the points raised by the two reviewers and the Editor, we revised the manuscript as much as we can. The details of the revision and answers for their questions are described in the revision notes. The modified points are indicated in **red**.

We also reconsulted the KN International to polish up English of the manuscript. Certificate of language editing is uploaded along with the revised manuscript. The modified points by English editing expert are indicated in **blue**. I deeply thank the Editor and you for giving us extra opportunity to improve the manuscript.

Sincerely yours,

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Revision notes

A. Responses to the comments raised by Editor

We deeply thank the Editor and you for giving us extra opportunity to improve the manuscript. we added the contents as indicated below.

Institutional review board statement: This case report was exempt from the Institutional review board standards at Kobe University Graduate School of Medicine and Hospital, Kobe, Japan.

Informed consent statement: The patient participant to the study provided informed written consent.

Conflict-of-interest statement: The authors declare no conflict of interest associated with this manuscript.

COMMENTS

Case characteristics

A 56-year-old male with locally advanced rectal cancer (LARC) developed preoperative rectal perforation in the midst of 5-FU-based preoperative chemoradiotherapy (CRT).

Clinical diagnosis

Colonoscopy and imaging tests resulted in a clinical diagnosis of LARC with direct invasion to adjacent organs and regional lymphadenopathy.

Differential diagnosis

Inflammatory associated rectal perforation

Laboratory diagnosis

Preoperative serum level of CEA was increased to 21.0 ng/mL (normal < 2.5).

Imaging diagnosis

The CT findings revealed rectal perforation with air-fluid around the left side of the seminal vesicle adjacent to the rectum.

Pathological diagnosis

A wide area of tumor tissue was replaced by necrotic tissue and fibrous tissue, suggesting that chemoradiation had been effective.

Treatment

The patient completed preoperative CRT after supporting emergency recovery.

Related reports

To our knowledge, only 6 cases of perforated LARC associated with 5-FU-based preoperative CRT have been reported.

Term explanation

There are no uncommon terms used in this manuscript.

Experiences and lessons

We share this case as important evidence for the treatment of LARC perforation in the midst of preoperative CRT.

Peer-review

This case report demonstrated that completing preoperative CRT after supporting emergency recovery may enhance the anti-tumor effect, resulting in a better prognosis.

B. Responses to the comments raised by Reviewer (Reviewer's code: 00028630)

The case report is well described and the references area exhaustive; although I am not very surprised to occur a perforation into an advanced rectal cancer during a preoperative chemoradiotherapy.

This case report demonstrated that completing preoperative CRT after supporting emergency recovery may enhance the anti-tumor effect. In addition, completion of preoperative CRT according to the original plan after supporting emergency recovery for CRT-related rectal perforation has never before been described. We believe that the establishment of a

standard treatment for CRT-related LARC perforation may help the prognosis.

C. Responses to the comments raised by Reviewer (Reviewer's code: 03668742)

Review of the manuscript entitled: "Local advanced rectal cancer perforation in the midst of preoperative chemoradiotherapy: A case report and literature review". Regarding the risk of locally advanced rectal cancer perforation, Takase et al. performed a literature review and a presentation of a case with the aforementioned perforation related to the treatment with chemoradiotherapy. This case study is a welcome reminder to clinicians about the risk of perforation after neo-adjuvant chemoradiotherapy. The case study is well reported and interesting to read. However, the subsequent literature review is not fully explained. The study lacks a description on the literature search and which databases were used. This should at least be reported if the authors wish to state the article as being both a case study and a literature review (the search strategy could be included in the description of table 1). The discussion segment is also too long. Sentences like: "Colorectal perforation is a life-threatening complication considered to be associated with a poor outcome" could easily be omitted. The manuscript needs linguistic revision before it can be made into a publication.

Regarding their suggestion, we agree with the Reviewers comments and we revised the discussion section and Table 1.

1. Discussion (page 6, line 26–27), we modified a sentence as indicated in red.

Radiation-related tissue injuries are well known to occur in the gastrointestinal tract, ~~with damage to the small bowel, colon and rectum.~~

2. Discussion (page 7, line 10–15), we deleted sentences and modified a sentence as indicated in red.

~~It is important to understand potential possible events including adverse effects by the combination of 5-FU-based drugs and radiation.~~

Colorectal perforation is a life-threatening complication ~~considered to be associated with a poor outcome~~. The causes of rectal perforation include fecal impaction, enema, and cancer and its therapy, including RT, chemotherapy and molecular-targeted therapy. Among them, rectal perforation from pelvic RT is an extremely rare adverse event. The mechanisms of radiation-related perforation, especially the difference in responses between normal rectal tissue and LARC tissue, remain elusive. ~~The background of RT-induced intestinal ischemic change is present on both sides.~~

3. Discussion (page 8, line 4–7), we modified a sentence as indicated in red.

~~A recent study reported that~~ Pathological and immunohistochemical analyses of various factors in colorectal tumor perforation ~~related~~ compared with non-perforated tumors showed significant associations of tumor location (~~higher left-sided and rectosigmoid junction-sided tumor~~) –and cell differentiation (~~higher well differentiated tumor~~)^[21].

4. Discussion (page 8, line 8–10), we added a sentence and modified a sentence as indicated in red.

~~We searched common literature search engines (PubMed, Medline, Google Scholar).~~ To our knowledge, only 6 cases of perforated LARC associated with 5-FU-based preoperative CRT have been reported ~~in the English literature~~^[20, 22, 23] (Table 1).

5. Discussion (page 8, line 15–16), we modified a sentence as indicated in red.

In recent years, various molecularly targeted agents, ~~such as the anti-vascular endothelial growth factor (VEGF) inhibitor bevacizumab,~~ have been used clinically for colorectal cancer.

6. Table 1 (line 18–19), we added a sentence as indicated in red. The following cases searched common literature search engines (PubMed, Medline, Google Scholar) through August 2016, using search terms related to rectal cancer, perforation and chemoradiotherapy.