April 5, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 25523-Revised manuscript.doc).

Title: Colostomy is a simple and effective procedure for severe chronic radiation proctitis

Author: Yuan ZX, Ma TH, Wang HM, Zhong QH, Yu XH, Qin QY, Wang JP, Wang L

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 25523

The manuscript has been improved according to the reviewers' comments:

1. Format has been adjusted according to the Guidelines and Requirements for Manuscript Revision-Retrospective Cohort Study.

2. Revision has been made according to the reviewer's comments

(1) Reviewer No. 3387566: This is a well-described and convincing study on the interest in treating patients with severe CRP using colostomy. More details on radiation treatment received and DVH especially on the rectum would be a plus. I have 2 questions: 1) what is the percentage of patients developing severe CRP? 2) Given that patients to whom colostomy is proposed are those presenting the more severe CRP, may it influence the strength of the effect observed on the quality of life?

Respond to the reviewer: Thanks for these good comments.

#1 We have added more details on radiation treatment in the first section of results in revised manuscript as follow:

"Cumulative radiation dosage of one patient was about 80 Gy, which included the

radiation for both sites of primary malignancy and invasive lymph nodes. The detailed radiotherapy for those patients with gynecological cancers, especially cervical cancer, was 25 rounds (2 Gy/round) of external beam radiation and 5-6 episodes (6 Gy/episode) of intra-cavity brachytherapy. Patients with prostate or rectal cancers received only external beam radiation".

#2 Because all of these patients received radiotherapy in other radiotherapy centers, the patients' dose-volume histogram (DVH) parameters were stored in these centers or missed, we can't get access to these detailed parameters. Patients were admitted in our GI specialized medical center just for treatment of chronic radiation proctitis. Therefore, we also can't calculate the percentage of CRP patients after radiotherapy because these patients who did not develop CRP will not visit our medical center. However, we have assessed about 200 CRP (from mild to severe CRP) patients who have admitted in our hospital since 2007, we identified 47 (24%) of severe CRP among them.

#3 As for the comment that more severity of colostomy group may influence the strength of the effect observed on the quality of life, we have explained this issue in the discussion section as follow:

"Although the colostomy group had more severe bleeding than the conservative group, which would bring selection bias, but on contrary, colostomy group had achieved dramatically better control of bleeding, higher increased hemoglobin level, and improved quality of life than conservative group. These results have shown the advantages of diverting colostomy in treating severe CRP bleeding than conservative treatments".

#4 All of the language in the manuscript has been polished.

Thanks again for these comments to improve this manuscript.

(2) Reviewer No. 2953710: This study is interesting because it reported a large series of patients treated with colostomy for CRP. However Authors should better explain: - the high percentage of fistula is related to the pathology (mainly female cancer?), or previous endoscopic biopsies or treatment with APC? - mentioning radiofrequency ablation, a new effective treatment with few complications - conservative treatment of fistulas is possible with Giant clip as OTSC.

Respond to the reviewer: Thanks for these comments and suggestions

#1 - the high percentage of fistula is related to the pathology (mainly female cancer?), or previous endoscopic biopsies or treatment with APC?

Response: because 44 (94%) of 47 CRP patients enrolled in this study were gynecological cancers in females, so most of fistulas were documented in females. While in most western countries, prostate cancers in males are the dominant population receiving pelvic radiation and CRP is mainly reported in prostate cancers[4, 12]. However, prostate cancers receive only external beam radiation including 3-dimensional conformal radiotherapy

(3D-CRT) and intensity-modulated radiotherapy (IMRT), and they don't receive intra-cavity brachytherapy, thus less fistulas are observed. In addition, according to our clinical practice, intra-cavity radiation can bring much more adverse effects including fistulas and other severe radiation-related complications than external beam radiation. (We have added this explanation into the last second section of the discussion)

In addition, it is true that endoscopic biopsies or treatment with APC in severe CRP, especially in those with deep ulcers may cause fistula. There is no significant difference of the percentage of previous endoscopic biopsies or treatment with APC among these two groups. However, during follow-up, patients in conservative group has received more topical formalin or APC treatments and developed more fistulas later, than these in colostomy group. Therefore, we suggested topical formalin or APC should be selected very cautiously in these severe CRP patients.

Furthermore, only one patient has endoscopic biopsy and it occurred after colostomy. This patient has obtained complete remission of bleeding and the biopsy sites were fully healed according to endoscopic observation.

Therefore, we think colostomy can reduce severe CRP complications than other treatment options.
(We have also added these discussions into the last section of the results and the first section of the discussion)

#2 - mentioning radiofrequency ablation, a new effective treatment with few complications - conservative treatment of fistulas is possible with Giant clip as OTSC.

Response: that is good comment. We have added the radiofrequency ablation (RFA) and related references into the first section of the discussion as follow:

"Recently, new radiofrequency ablation (RFA) in treating CRP has been introduced and improvement in hemoglobin and decrease in clinical symptoms are observed[31, 32]. But most of RFA studies are based on retrospective case series without controls and current data are scare, prospective trials of RFA should be conducted in the future to validate its efficacy and application in severe CRP patients"

As for Giant clip as OTSC for fistula secondary to radiation proctitis, we did not search out the literatures of this method in treating CRP perforation, and we did not use it before in CRP patients. Actually, we've tried topical revision and skin flap transplantation for some CRP fistulas previously. But the efficacy is very limited and new fistula can occur quickly, due to poor healing capacity of irradiated mucosa and bacterial infection from fecal stream,

which leads to failure of these treatments. (We have added these explanations into the third section of the discussion).

#3 All of the language in the manuscript has been polished.

Thanks for these advices and comments to improve our manuscript.

Sincerely yours,

Lei Wang

Lei Wang, MD, PhD, Professor
Department of Colorectal Surgery, The Sixth Affiliated Hospital,
Sun Yat-Sen University, Guangzhou, China;
Address: No. 26 Yuancun Erheng Road, Tianhe District,
Guangzhou 510655, China.
Tel: (86) 020-3876-7131; Fax: (+86) 020-3825-4221.
E-mail: leiwangyinhu@163.com or wangl9@mail.sysu.edu.cn.