ANSWERING REVIEWERS

March 6, 2014,

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Revised manuscript 9205 clean.doc).

Title: Abdominoperineal excision following preoperative radiotherapy for rectal cancer: unfavorable prognosis even with negative circumferential resection margin.

Author: Lin Wang, Guoli Gu, Zhongwu Li, Yifan Peng, Jin Gu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9205

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

A. To reviewer 00057479:

We very appreciated your comments. As you mentioned, the decision making for an APE was very complicated in clinical practice. We did not make the decision only concerning the height of tumor but also refer to preoperative imaging and intraoperative findings. Our center was the earliest unit that introduced concept of neoadjuvant radiotherapy into our country. Actually our local recurrence rate was at or even below the LR level of many published article. We hope you reconsider our article for publication in future.

B. To reviewer 00058378:

Thank you for your kind comments. We revised the article as followed:

1. The decision making for an APE is explained in Method section of present manuscript.
2. There were two regimens of neo-RT/CRT in our center; one is 30Gy/10f for higher efficiency and lower cost, according to the developing fact of PR China.
   Another one is IMRT GTV 50.6Gy/CTV 41.8Gy/22f+concurrent Capecitabine. The IMRT regimen has high ypCR and low toxicity rate but with increased cost. The initial result of IMRT from a Phase II study will be orally presented by me in ASCRS annual meeting 2014, S36 in rectal cancer session, Hollywood, Florida, US.
   In our center, interestingly, traditional 45-50.4Gy in 25-28 fractions regimen was rarely used. We made a big jump from simple 3DCRT(30Gy) to IMRT, after we bought the new Varian radiation accelerator.
3. The stage in table was post-radiation pathological stage (ypTNM), not pre-staging. The pre-stage before radiation is all stage II(18.8%) or III (81.2%), which is demonstrated in patients' morphology.
4. According to NCCN guideline, all patients were encouraged to receive 5FU based or Capecitabine Chemotherapy. However, many of patients went back to their home province and we cannot get sufficient information. We will improve our follow-up work in future.
5. We made some alteration in language.

C. To reviewer 00043413:

Thanks for your kind comments. We will polish our language.

D. To reviewer 00041968:

Thank you for kind comments. We revised the article as followed:

1. The abbreviations had been elaborated in the new version of manuscript.
2. We used 0.1 as cutoff value in multivariate survival analysis, which was widely accepted. In other section of analysis, 0.05 is our cutoff value.
   The SPSS software is updated to Version 22 for mac, from IBM Company.
   In many colorectal cancer researches, there is a trend that using 3-year DFS instead of 5-year OS, for more efficient analysis with equal power. The related reference is as followed and also be quoted in the new version of our manuscript.
   "***de Gramont A, Hubbard J, Shi Q, et al. Association between disease-free survival and overall survival when survival is prolonged after recurrence in patients receiving cytotoxic adjuvant therapy for colon cancer: simulations based on the 20,800 patient ACCENT data set. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010; 28(3): 460-465 [PMID: 20008641 PMCID: 2815708 DOI: 10.1200/JCO.2009.23.1407]***"
3. It was distant metastasis which we wanted to clarified in the exclusive criteria, and we amended it.
4. We replaced "oncologic outcome" with "patient survival", and replaced "tumor height =" with "level of tumor". We also made some elaboration on decision making based on BMI, gender and level of tumor.

E. To reviewer 00044067:

Thank you for your kind comments. We revised the article as followed:

1. We consult statistician and think the limited events number is not sufficient support multivariate analysis in local-recurrence free survival. We clarified this in the new version of manuscript.
2. We categorized mid and low rectal cancer only basing on the level of tumor. But from our clinical experience, this cutoff value was not very accurate and with many variations.
   For instance, a 5cm posterior tumor will have significant longer muscle tube than a 5cm anterior tumor after releasing the rectum in TME procedure. There were also many patients with narrow pelvis, especially in male. This possible reason had been elaborated in the new version of manuscript.
3. We also performed RFS and DFS in all patients and also in low rectal cancer group, the results is similar, to reveal the worse prognosis following APE.

3 References and typesetting were corrected

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

Sincerely,

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