

June 4, 2016

Dear Dr. Yu and Reviewers,

We thank you for considering our manuscript entitled, "Endoscopic and non-endoscopic approaches for the management of radiation-induced rectal bleeding" for publication in the *World Journal of Gastroenterology*. We thank the reviewers for taking the time to review our manuscript and for their comments and suggestions. We believe that our modifications in response to these comments have significantly enhanced the clarity and flow of the manuscript. We have addressed the reviewer comments below on a point by point basis. The reviewer comments are in standard font and our responses are in bold.

Reviewer #1:

Outstanding and comprehensive review article. There are only minor grammatical and medical terminology errors correctable with minor revision.

We thank the reviewer for this comment. We have enlisted other authors to proofread the manuscript for grammatical and medical terminology errors. We believe these revisions have greatly enhanced the clarity of our article.

Reviewer #2:

Overall an excellent review of an important topic. Some suggestions below to further strengthen this manuscript. Suggest adding additional coauthors to better edit and proofread manuscript

We thank the reviewer for this suggestion and have added additional authors as noted above.

1) page 3 line 4 abstract typo: medical instead of medial

We thank the reviewer for this comment and have corrected this typo.

2) page 3 line 9 abstract type: plasma instead of plasm

We thank the reviewer for this comment and have again corrected this typo.

3) page 3 abstract: delete specific reference to radical surgeries in abstract because this is exceedingly rare

We agree with the reviewer that radical surgeries are exceedingly rare in the management of radiation proctopathy and have therefore removed this reference from our abstract.

4) page 8 prevention: perhaps "errant dose towards unwanted targets" can be expressed more artfully. Most radiation oncologists refer to "planning target volume" vs. "organs at risk"

We thank the reviewer for this suggestion and have modified the sentence as follows:

“Reducing the radiation dose to the organs at risk has historically been achieved through physical means.”

5) page 8-9 prevention: there is discussion of small bowel but the focus of the review is on rectum

We agree with the reviewer that the scope of our review is on radiation proctopathy. We have therefore removed the discussion on small bowel injuries. The paragraph in question is reproduced below:

“Reducing the radiation dose to the organs at risk has historically been achieved through physical means. Though simple, changing the physical measures of patient setup, such as supine versus prone placement or daily treatment with a full bladder versus an empty bladder, has been shown to have an impact on dosimetric and clinical outcomes[29]. A study reported by Bayley et al showed that for patient’s treated for prostate cancer, the supine patient position decreased dose to rectal wall compared to the prone position[30]. More invasive techniques of physically displacing organs at risk have been developed. For men with prostate cancer, a 50% dose reduction to the rectal wall has been achieved through a quick, outpatient trans-perineal injection of a collagen spacer[31]. This spacer increased the distance between the rectal wall and the prostate gland, thus allowing additional dose fall off and sparing of the rectum.”

6) page 10-11: it is fair to say that amifostine is not widely used for pelvic malignancies due to toxicity resulting in marginal risk:benefit ratio.

We agree with the reviewer that the significant toxicities associated with amifostine have limited its clinical adoption. We have modified this paragraph by adding the following:

“Despite this data from several randomized trials, the routine adoption of amifostine for the prevention of radiation proctitis remains limited. This is likely due to the toxicities associated with amifostine, particularly severe hypotension, which limit the therapeutic ratio derived from its use.”

7) page 12 typo: English instead of English

We thank the reviewer for this ccorrection.

8) Hyperbaric oxygen: please include new randomized trial in Lancet Oncology (Glover, Lancet Oncol epub 2015)

We thank the reviewer for this suggestion and have added this trial to our discussion of hyperbaric oxygen. This revision is reproduced below:

“However, a recent trial conducted by Glover et al reported results contradicting these previous studies [83]. This trial randomized 88 patients with chronic bowel dysfunction following pelvic radiotherapy to either HBO or sham control. HBO failed to significantly improve patient-reported bowel quality of life or rectal bleeding compared to sham control. Given the mild and transitory common side effects of HBO such as, anxiety, otic barotrauma and temporary myopia, as well as its

questionable efficacy it can be considered an alternative to more invasive treatments in a patient failing medical management[84].“

9) References: consider including the two NEJM papers on QOL after prostate treatment (Resnick, NEJM 368: 436, 2013; Sanda, NEJM 358: 1250, 2008)

We thank the reviewer for this suggestion and have incorporated these two studies into our introduction on page 5. We have added the following:

“Patients receiving pelvic radiation will often experience an acute temporary worsening of rectal symptoms with a return to baseline by 6 months after therapy [4,5]. Radiation dose to the rectum can less often result in the development of late complications such as radiation proctitis, which is broadly defined as epithelial damage to the colon due to radiation treatment[6].”

10) References: did you include the Lancet Oncology study (Andreyev, Lancet Oncology 382: 2084, 2013)

We thank the reviewer for this additional reference. We have incorporated a brief discussion of this trial into our introduction of treatment approaches on page 6. This revision is reproduced below:

“Treatment algorithms incorporating many of these aforementioned interventions have been previously proposed and shown to be efficacious in improving patient-reported quality of life[47].”

11) suggest pruning some of these references. 139 seems a bit high

Overall, very nice and comprehensive review!

We thank the reviewer and have reduced the number of references in our article to 120 from 139.

Once again, we thank the reviewers for taking the time to critique our study. We hope that the modifications that we have made in response to the reviewer suggestions have now made the manuscript suitable for publication in *World Journal of Gastroenterology*. Thank you again for considering our manuscript for publication.

Sincerely,

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