

Li-Sheng Ma

President and Company Editor-in-Chief

World Journal of Gastrointestinal Surgery

25th March 2017

Dear Dr Ma,

Please find attached the revised version of manuscript titled “Advances in surgical management for locally recurrent rectal cancer: how far have we come?”, which we would like to resubmit for publication in the World Journal of Gastroenterology.

Thank you for your feedback and below here is the point-to-point responses to each of the comments from the reviewers:

Responses to comments from Reviewer #1:

More precised definition on “distant metastases”, “extensive pelvic sidewall involvement” and ‘poor performance status’ seen in Table 1.

Response: Correction has been made to Table 1. Table 1 outlines conditions that were previously deemed contraindication to surgery if there is local recurrence. However, with improvements in surgical techniques and preoperative intervention, we are seeing an increase in curative resection being offered to patients as an option. This is the main crux of this article; to educate readers on recent advances in surgical approach.

Poor performance status remains an absolute contraindication to surgery. It is defined objectively with various assessment tools (e.g CPEX test) or grading systems (e.g Karfonsky or ECOG performance status), depending on institution practice.

What is not mentioned in these complex situations are simultaneous hepatic resections and timing of preoperative chemotherapy. If the patient has operable liver metastases should these be resected during the same operation? When should the presence of a KRAS mutation be determined?

Response: We have added a section to further discuss preoperative planning and multimodality treatment. In this segment, we discussed approaches to LRRC with synchronous operable metastases. The optimal sequence of surgery remains to be clarified. Both synchronous and staged approaches are reported; none have been proven to be more superior to than the other. It is the authors’ preference to treat the local recurrence ahead of metastectomy.

Comprehensive discussion on the preoperative chemotherapy is beyond the scope of this article; it is not the main objective of this review article. Nevertheless, we have included a concise overall view of preoperative chemoradiotherapy used in LRRC.

Technical considerations on reconstruction with myocutaneous flap. Preoperative and intraoperative counselling with a plastic surgeon is important because rectus abdominis from

the other side should be utilized if colostomy is formed. It is better to mobilize flap and close the donor site and then perform colostomy to reduce possibility of surgical site infections of the donor site. And Then when should radiotherapy be used because it can have negative influences on the flap survival? To One should consult Bruketa T et al. Rectal cancer and Fournier's gangrene – current knowledge and therapeutic options. One should also see *Also* what options are available if such patients present with acute abdomen due to complications of recurrent rectal cancer.

Response: We agree with the reviewer on the technical consideration and have included his/her suggestion in the discussion. The use of radiotherapy has been added under the Multi-modality Treatment Approach section of the article. This article focuses on the complex surgical approaches in resecting local recurrent tumour; discussion on options for patients presenting with acute abdomen is therefore not applicable here. We do not advocate to resect the locally recurrent tumour without thorough preoperative investigation and it should not be carried out in an emergency setting.

It is written: “ Figure 4: Posterior recurrence involving the presacral fascia (outline in blue)”
The line is not blue but RED.

Response: The correction has been made.

Reviewer #2

The paper requires extensive grammatical and English revision.

Response: The grammatical error pointed out by the reviewer has been corrected. We have had it proof-read again and have further refurbished any grammatical and spelling lapses.

The table showing contraindications: Isn't primary disease stage 4 the same as that group with Distant metastases

Response: Stage 4 primary disease refers to metastasis seen when patient first had rectal cancer. 'Distant metastases' in this context refers to patients presenting with LRRC and synchronous distant metastases.

In the reference to Royal Marsden Hospital, this is not necessary to state.

Response: The hospital name has been omitted in the article.

Reviewer #3

1. Are distant metastases always a contraindication for pelvic exenteration? What about a small liver or lung lesion, stable under systemic chemotherapy. Performing the exenteration will control the local progression and avoid complications. Please comment.

Response: Patients with inoperable distant metastases would be considered for palliative treatment. We agreed with the reviewer that isolated, operable metastases should be offered curative resection in highly selected patients. These considerations have been addressed in the article.

2. In how many cases was a bladder involvement proven by histology? Can this be reliably investigated preoperatively?

Response: We have outlined the use of various preoperative imaging modalities to improve our assessment on invasion of tumour to pelvic structures. MRI is highly sensitive in assessing invasion to central pelvic structure but may have difficulty reporting tumours affecting the pelvic sidewall. We do not have data on bladder involvement proven by histology. The other option to determine bladder involvement is via frozen section analysis done intraoperatively.

3. Is there any data regarding the quality of life after pelvic exenteration with sacrectomy/

Response: There are various studies reporting on quality of life after pelvic exenteration. The study population is heterogenous and data specifically on pelvic exenteration with sacrectomy is rare. In our opinion these reports add no value to our discussion.

4. Does neoadjuvant radiochemotherapy play a role?

Response: Yes, it does. Discussion on this topic has been added to the article.

5. Please stress that the best survival data is for anastomotic recurrence, this should be always a straight decision to operate?

Response: We agree with the reviewer and this fact has been emphasized in the article.

6. May preoperative embolization of pelvic arteries facilitate a reduced intraoperative morbidity and bleeding?

Response: Preoperative embolization of pelvic arteries can be used as an adjunct. We have included this in the article.

7. Do latissimus dorsi flaps play a role? In some patients usual use flaps cannot be used.

Response: Yes, it does. Its use has been illustrated in Figure 3 of the article. A brief discussion on this topic has been added to the article.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in the World Journal of Gastroenterology.

We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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