

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Surgery*

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Title: Surveillance strategies following curative resection and non-operative approach of rectal cancer: how and how long? Review of current recommendations

We really thank the reviewers for the very nice comments and moreover for the important consideration and issues raised. We have tried to address properly all the issues in order to satisfy all the requested changes. We hope that all our changes and answers are sufficiently satisfying and make our paper suitable for publication.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This review of follow-up for rectal cancer is a retrospective study of sufficient follow-up trials and protocols with a sufficient literature background. In addition, there is no consensus on follow-up after treatment for colorectal cancer. This review provides available evidence for this phenomenon and has special significance for future guidance.

Response to Comments: We really thank the reviewer for the kind comments. We agree that, even though follow up programs following rectal cancer treatment are widely accepted and adopted, there is still no consensus regarding which test should be performed, the time schedule, the frequency and the duration of surveillance. The impact on survival is not clear also, since salvage surgery following recurrence detection is not guaranteed. Current published guidelines and recommendations from the most authoritative specialty societies have been reviewed in order to provide evidence for future guidance.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: First, this is an interesting review focus on the surveillance strategies for rectal cancer patients after total mesorectal resection as well as patients with non-operative management, which is a hot topic in the era of neoadjuvant chemoradiation. This review provides systemic summary of evidence based on guidelines and clinical studies. Second, this review lists a series of clinical examinations, such as DRE, CT, etcs. As the functional screening, such as PET-MRI, or in vivo imaging using tumor specific isotopes might be more proficient. Third, it would be of importance to introduce the detailed definition of non-operational strategies, such as wait and watch, for cCR patients, or curative radiation, etcs. Recent literatures demonstrated that accumulating evidence provided in the preference of wait and watch in certain selected patients with intensified chemoradiation.

Response to Comments: We really thank the reviewer for the important considerations and issue raised. We have listed and reviewed all the tools adopted for follow up including clinical examination, measurement of CEA, endoscopy and CT scan. All major specialty societies in the published guidelines include these means which are actually largely adopted considering the cost benefit ratio. For this reason a large part of the manuscript overviews the literature regarding these tests. However we have tried to reduce the first part of the manuscript especially the introduction and the text regarding physical examination and blood tests.

It should be noted that, even though rectal cancer is associated to local recurrence more often than colon cancer, a strict local evaluation with rectosigmoidoscopy associated or not to endorectal ultrasound or MRI is suggested only in the NCCN and ASCR guidelines. There is no mention of any functional imaging in any published guidelines. Only NCCN suggests the adoption of PET-CT in case of rising CEA. Furthermore, we have been able to identify 17 randomized clinical trials evaluating different follow-up strategies and only the study by Sobhani included PET in the intensive arm [Sobhani I, Tiret E, Lebtahi R, Aparicio T, Itti E, Montravers F, Vaylet C, Rougier P, Andre T, Gornet JM et al. Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer. *Br J Cancer* 2008, 98(5):875-880]. This study published in 2008 showed early detection of recurrence by 18FDG-PET leading to a survival benefit due to increased curative reoperation. Indeed, the role of PET imaging in rectal cancer follow up

remains marginal. However we agree with the reviewer about the importance of functional imaging such as PET, PET-CT and the more recent PET-MRI. Particularly, extraluminal local recurrence following TME or Non-Operative Management of rectal cancer is very difficult to detect. Curative resection is the only real option for these patients and early diagnosis of recurrence in this setting is crucial. The recent introduction of FDG-PET/MRI seems to be promising. As suggested, we reported the published literature about this novel hybrid technique and added it to the main text in the PET scanning chapter. Specifically we reported the experience from Plodeck et al that published two papers about the role of FDG-PET/MRI in pelvic recurrence of rectal cancer. The first paper published in 2019 reported the first experience with a sensitivity and specificity of 94% [Plodeck V, Rahbari NN, Weitz J, Radosa CG, Laniado M, Hoffmann RT, Zöphel K, Beuthien-Baumann B, Kotzerke J, van den Hoff J, Platzek I. FDG-PET/MRI in patients with pelvic recurrence of rectal cancer: first clinical experiences. *Eur Radiol.* 2019 Jan;29(1):422-428]. The second paper published in 2021 compared PET/MRI to MRI alone in the diagnosis of pelvic recurrence: sensitivity and accuracy of PET/MRI were superior; furthermore PET/MRI increased confidence in diagnosis or exclusion of local recurrence [Plodeck V, Platzek I, Streitzig J, Nebelung H, Blum S, Kühn JP, Hoffmann RT, Laniado M, Michler E, Hoerück S, Zöphel K, Kotzerke J, Fritzmann J, Weitz J, Radosa CG. Diagnostic performance of ¹⁸F-fluorodeoxyglucose-PET/MRI versus MRI alone in the diagnosis of pelvic recurrence of rectal cancer. *Abdom Radiol (NY).* 2021 Nov;46(11):5086-5094]. Even though, PET imaging specially PET/MRI may play an important role for detection of pelvic recurrence, the diffusion and cost clearly limits its adoption and at the state of art its introduction as routine diagnostic method is unrealistic.

Finally considering the importance of non-operative treatments of rectal cancer and the increased adoption of these strategies we dedicated an entire chapter to this topic. As requested, we enriched the manuscript with a more detailed definition of cCR. We choose the definition from the paper of Barina et al. published in 2017 [Barina A, De Paoli A, Delrio P, Guerrieri M, Muratore A, Bianco F, Vespa D, Asteria C, Morpurgo E, Restivo A, Coco C, Pace U, Belluco C, Aschele C, Lonardi S, Valentini V, Mantello G, Maretto I, Del Bianco P, Perin A, Pucciarelli S. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. *Tech Coloproctol* 2017 21:633-640]. In this multicenter observational study the cCR was defined as follow: the absence of any palpable tumor at digital rectal exploration and no visible lesion (flat scar or teleangiectasia) at endoscopy are the main criteria complemented by the absence of residual tumor and metastatic

lymphonodes on MRI. We also added the experience of total neoadjuvant therapy (TNT) reporting the paper from Garcia-Aguilar that in a prospective randomized phase II trial was able to demonstrate better result in terms of tumor response (organ preservation in up to 53% of patients) following application of radiotherapy and full systemic chemotherapy before surgery [Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, Verheij FS, Omer DM, Lee M, Dunne RF, Marcket J, Cataldo P, Polite B, Herzig DO, Liska D, Oommen S, Friel CM, Ternent C, Coveler AL, Hunt S, Gregory A, Varma MG, Bello BL, Carmichael JC, Krauss J, Gleisner A, Paty PB, Weiser MR, Nash GM, Pappou E, Guillem JG, Temple L, Wei IH, Widmar M, Lin S, Segal NH, Cerce A, Yaeger R, Smith JJ, Goodman KA, Wu AJ, Saltz LB. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. *J Clin Oncol.* 2022 Aug 10;40(23):2546-2556]. In this setting we also reported the role of FDG-PET/MRI in restaging patients deemed to have a cCR following TNT. The recent paper from Ince et al in 2022 reported an accuracy of 100% of FDG-PET/MRI evaluating residual disease adding a significant value in restaging and enrolling patients in non-operative management [Ince S, Itani M, Henke LE, Smith RK, Wise PE, Mutch MG, Glasgow SC, Silviera ML, Pedersen KS, Hunt SR, Kim H, Fraum TJ. FDG-PET/MRI for Nonoperative Management of Rectal Cancer: A Prospective Pilot Study. *Tomography.* 2022 Nov 9;8(6):2723-2734].

We hope that these changes are satisfying.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Follow up programs after rectal cancer curative treatment have been widely accepted. There are several guidelines like ASCO, NCCN, ESMO for reference. Regarding which test should be performed, the time schedule, the frequency and the duration of the surveillance, I think it is not a confused option. Even if the guidelines are not consistent with each other at some respects, they are generally practical. This review provide an overview of recommendations on this topic, however, the earlier part of the manuscript is verbose. The medical history and physical examination, CEA, liver function test, and introduction should be massively compressed.

Response to Comments: We really thank the reviewer for the kind suggestions. We

agree that the guidelines are practical but, although the topic is apparently clear and doubtless, our review has shown many discrepancies between the different scientific societies and how often the same guidelines are disregarded in clinical practice. Even active member of scientific societies do not follow the recommended guidelines [Giordano P, Efron J, Vernava AM, 3rd, Weiss EG, Nogueras JJ, Wexner SD. Strategies of follow-up for colorectal cancer: a survey of the American Society of Colon and Rectal Surgeons. *Tech Coloproctol* 2006, 10(3):199-207]. Although it is well known that rectal cancer has a high local recurrence rate only ASCO, ASCR and NCCN suggest a local follow up with frequent rectoscopy and only ASCR and NCCN suggest the possible association with MRI and Endorectal USS. No scientific society takes into account the ever-growing issue of patients enrolled in non-operative treatments. Since our paper tries to address and clarify this clinical setting, we believe that our review adds something to the current literature. We agree that the first part of the article is unnecessarily repetitive and its length may bore the reader and risks dispersing his attention. For this reason, as suggested, we have significantly reduced the text: the introduction has been shortened significantly and the follow up grounds deleted and integrated into the introduction. Medical history, physical examinations and CEA have been reduced while liver function tests have been completely removed since they are not adopted by any societies. We hope that these changes are satisfying.