

February 27, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8325-review.doc).

Title: Long-term results of rectal cancer treated with neoadjuvant chemo-radiation and laparoscopic mesorectal excision and no adjuvant therapy for complete responders

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8325

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

Reviewer 1:

The manuscript entitled “Long-term results of a “wait and see” strategy for rectal cancer achieving a pathological complete response after chemo-radiation and laparoscopic mesorectal excision” which is presented by X. García-Albéniz and co-workers is a retrospective database analysis of rectal cancer patients who received neoadjuvant treatment. Those, who experienced complete remission, were not given adjuvant treatment and showed a very good outcome. A validation cohort is provided. In general, the study is well performed, the manuscript well written and easy to follow. Some comments have to be made.

Major

1. Data how the pathological diagnosis was made are incomplete: Were routine diagnoses used? Was central pathology reading performed? The number of complete remissions is comparably high – how much effort was undertaken to find residual cancer foci (e.g. embedding of the whole tumor area, step sections, immunohistochemistry)?

We have provided further detail in the text (lines 68-70) about the personnel involved, staining and protocol used.

2. You group the patients into the following groups: complete response, intermediate response, and poor response. In general, I believe this is feasible, but a rational and/or reference for this approach is mandatory. In addition, I deeply miss standard regression grading (e.g. according to Dworak) – why was it not performed? In my eyes this is necessary to enhance the comparability with other studies.

We agree with the reviewer that the regression grading according Dworak grade would be also useful. Unfortunately this grading was not prospectively analyzed in any of the cohorts. Our conclusions will thus only apply to those patients evaluated using the same approach as ours.

3. I feel, the validation cohort is not “ideal” as it is a cohort with rectal cancer patients who received

neoadjuvant therapy, but not a cohort in which ypT0N0 patients did not receive adjuvant therapy. In this central aspect (please compare the title of your submission), you compare your 26 patients with just one single case, and this cannot, strictu sensu, be called “validation”.

We agree with the reviewer. We have changed the term “external validation” by “external reference” across the manuscript.

Minor

1. The identification number of the specific ethics committee vote is missing, please provide.

The protocol followed by the main cohort was approved as standard practice by the tumor board of Hospital Clinic and the IRB of the same institution approved it as a non-experimental practice, waiving full review.

2. In the material and methods section you refer to exclusion criteria, but inclusion criteria are not provided here (only in the introduction), please present the inclusion criteria where appropriate.

Following reviewer’s suggestion we have added this (lines 52-53).

3. In the results section you refer to the median number of harvested and/or identified lymph nodes and give the range. We would also like to know about the percentage of cases in which you achieved a minimum of twelve nodes: in the entire cohort and in the three groups (table 2).

Following reviewer’s suggestion we have added this (lines 128-129 and table 1).

4. I like that you “mainly” have rounded the percentages to integers which is reasonable. But you have not done this consequently everywhere in the results section, please correct.

This has been corrected throughout the manuscript.

5. In the second paragraph of page 11, relapse is noted in 42 (43%) patients in the group with poor response, but percentages are not provided for the groups with intermediate response (this would be 6%, if I calculated it correctly) and complete response (4%). Looking at these so far missing percentages you see that the rate of relapse is also low in the group with intermediate response, how do you explain this? Should these patients receive adjuvant therapy – why?

Percentages have been added as suggested.

We agree with the reviewer that the rate of relapse in the group of intermediate and good responders is very low. Our interpretation is that those tumors that respond to therapy probably have themselves a lower capacity to metastasize. Actually, the reviewer has touched here the main point of the article: given that response to neoadjuvant therapy predicts relapse and it can be assessed very precisely before deciding on adjuvant therapy, this can be used to select those patients candidate for further chemotherapy. In the current manuscript we show that those with complete response do not need adjuvant chemotherapy to have an excellent prognosis.

6. The first sentence of the discussion appears to be a bit misleading. What you have done is a retrospective data analysis of a (in the best case) prospectively generated database, but not something like a “prospective study”.

We cannot agree with the reviewer. The classification of studies into prospective or retrospective sometimes is not straightforward, but we believe that this is not the case here. We designed the protocol and then implemented the study, recording the information prospectively. According to the

reference book "Modern Epidemiology" (Rothman KJ, Greenland S, Lash TL, 3rd edition, page 96): "when the person-time [i.e. follow-up of our patients] accumulates after the study begins [i.e. enrollment into the cohort because of rectal cancer diagnosis], it is said to be a prospective study; in this situation, exposure status [i.e. tumor response] is ordinarily recorded before disease occurrence [i.e. relapse or death]" which is exactly the case in our study.

7. Table 1: Please also provide the terms "complete response", "intermediate response", and "poor response" in the heading of this table to increase the readers' understanding.

Following reviewer's suggestion, we have added this information in the tables.

8. The DOI-numbers are missing in the reference list (journal requirement).

We apologize for this. References have been reformatted according to WJG guidelines.

Reviewer2:

No comments provided.

Reviewer 3:

García-Albéniz et al. conducted a clinical study regarding long-term results of patients with ypT0N0 after conventional CRT and laparoscopic mesorectal excision without adjuvant therapy by analyzing 176 patients were treated with induction CRT and 170 underwent total mesorectal excision. They found that after a median follow-up of 58.3 months, patients with ypT0N0 have a 5-year disease-free survival and overall survival rate of 96% (95% CI 77 to 99%) and 100% (95% CI not estimable) respectively. The degree of pathological response is an important predictor of DFS and OS in both cohorts. Therefore, they concluded that withholding the adjuvant chemotherapy from those patients achieving a complete response after standard neoadjuvant CRT and laparoscopic mesorectal excision, if treated by an experienced multidisciplinary team, might be a reasonable option. Though this paper is relatively interesting and informative; however, there are a lot of criticisms and have the following comments that the authors need to address before the manuscript is suitable for publication.

Major Compulsory Revisions:

1. The major flaw was the definition of the response as complete response, intermediate response and poor response by authors' own standards, but not according to common used criteria such as based on a standardized tumor regression grading (TRG) as described by Dworak et al. (O. Dworak, L. Keilholz, A. Hoffmann, "Pathological features of rectal cancer after preoperative radiochemotherapy," International Journal of Colorectal Disease, vol. 12, no. 1, pp. 19-23, 1997.).

See response #2 to reviewer #1

2. In the Patients and Methods section, exclusion criteria for CRT treatment into the study were; (i) early stage (cT1-2N0), but in Table 1, 2 patients were classified into cT2N0?

These two patients were treated because their tumors were located in the low rectum and we considered that, despite staged cT2N0, the risk of local relapse without neoadjuvant chemo-radiotherapy was too high. A clarifying note has been added to table 1.

3. Any patient develops distant metastasis after pre-operative CRT? It is estimated approximately 3-5% of locally advanced rectal cancer patients would occur.

Lines 153 to 165 describe the patterns of relapse. If the reviewer refers specifically to the period of time between CRT and surgery, patients are not re-staged during this period in standard practice.

4. In table 2, baseline CEA level and days of admission following surgery were also predictive for DFS; in table 3, baseline CEA level was predictive for OS. But how to category studied patients into 2 groups of baseline CEA level and days of admission following surgery respectively should be addressed in more details in the text.

CEA and days of admissions have been entered as continuous variables in the model. For CEA a quadratic term (see footnote in tables 2 and 3) has been added to add flexibility to the adjustment. A clarification has been added in line 114.

5. Regarding statistical analysis paragraph, multivariate analysis was built with those variables with a p-value < 0.10 in the univariate analysis. Why multivariate analysis was not built with those variables with a p-value < 0.05 in the univariate analysis as the common used criteria.

Using the proposed criterion the HR for OS of the main exposure (ypT1-2N0 vs. ypT3-4/N1-2) is 0.29 (95% CI 0.11-0.76, p=0.0121) and the HR for DFS is the same because the same variables are selected.

6. In Discussion section (page 16): However our study has a long follow-up and it is the first evaluating the natural history of patients after CRT without adjuvant therapy and included all patients with > cT3, mid and low rectal tumors younger than 85 years evaluated in this period, reflecting a non-selected population of patients. But in table 1, median distance from tumor to anal margin is up to 15 cm, upper rectal cancer patients were actually included in the current study.

The percentage of patients with upper rectum was low. Median distance ranges between 5 to 8 cm (the upper range was 15 cm). We believe with the current knowledge, that if staging was done with MRI instead of ultrasound endoscopy, the majority of these cases will probably be located under 15 cm from the anal margin.

Minor Essential Revisions:

1. Histologic grade, lymphovascular invasion and perineural invasion are suggested to be analyzed simultaneously in the revised manuscript.

Unfortunately we do not have this information in the database.

Reviewer 4:

I appreciate the opportunity to review this study. A few comments/questions:

1. You have performed surgery between 5-8 weeks. Prior studies have differences in outcomes based on this, did you?

Unfortunately we did not record this information. We are aware that previous published data have observed an increment of down-staging in patients with delayed surgery.

2. More than anything, I disagree with your title. Wait and see with rectal cancer is traditionally used for patients who get a complete clinical response and then are not offered therapy. I think this confuses the population, the methodology and you need to change this by removing this from the title and in the manuscript.

According to reviewer comment the title has been changed to "Long-term results of rectal cancer treated with chemo-radiation and laparoscopic mesorectal excision and no adjuvant therapy for

complete responders."

3. Several errors in grammar and punctuation are present. Missing periods, misspellings. Please re-review.

We apologize for the errors. We have revised and corrected the whole manuscript.

4. Please clarify if the type of surgery (LAR vs APR) was in your multivariate analysis of DFS and OS. If not, it must be.

The type of surgery was not associated neither with DFS nor with OS. Its addition to the multivariate model did not change the estimate of the main exposure (type of response) and was therefore not entered in the final model to maximize efficiency.

5. The discussion is not focused. Please have each section divided up by a thought (DFS, OS) then review in light of your findings and the literature.

We have revised the discussion following the reviewer suggestion.

3 References and typesetting were corrected

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

Sincerely yours,

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