

January 17, 2024

Andrzej S Tarnawski, DSc, MD, PhD,
Editor-in-Chief
World Journal of Gastroenterology

Dear Prof. Tarnawski:

We are pleased to submit our revised manuscript, entitled "Stage at Diagnosis of Colorectal Cancer Through Diagnostic Route: Who Should be Screened?" (Manuscript NO. 91266), for consideration for publication in *World Journal of Gastroenterology*.

We appreciate your feedback and the reviewer's comments concerning our manuscript. The comments aided us in improving our manuscript. Our point-by-point responses to the reviewer's comments are appended to this letter. We believe that our revisions have improved the manuscript significantly.

We hope that the revised manuscript can now be approved for the next step in *World Journal of Gastroenterology*. Please contact us if you have any further questions or require any additional information. We look forward to hearing from you soon.

Sincerely,

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Point-by-point responses to the reviewer's comments on our manuscript (ID: 91266) entitled "Stage at Diagnosis of Colorectal Cancer Through Diagnostic Route: Who Should be Screened?"

Thank you for reviewing our manuscript and important suggestions. We have provided point-by-point responses to your comments below.

1. Comments from Reviewer 1:

This is a very informative and important article. Colorectal ca screening is an important public health tool and has vast health and cost implications to the society. The persistent problem with screening is acceptability by the population as well as to some extent availability and access to it for some disadvantaged demographics. 100% utilization although ideal would always be unachievable. This article explores a novel idea to address this problem by identifying a demographic who stands to benefit significantly from colorectal ca screening, ie people with infrequent contact with healthcare institutions. The article has demonstrated convincingly that this population presents with a higher stage of colorectal cancer at statistically significant higher rates than the people presenting for routine screening as well as those who make frequent contact with health care facilities. Formulation of policies to focus screening efforts to this population could therefore be beneficial. Such a policy would however need to address the problem of acceptability and access which is at the core of the problem. This population demographic, i.e. the patients who infrequently use healthcare facilities do so because either they do not have means, access to utilize healthcare facilities or sometimes are circumspect of modern healthcare. By focusing on these patients, as a policy matter, would hopefully overcome the basic issues of accessibility and access.

Response: We sincerely acknowledge and value your recommendations for our manuscript. As you rightly pointed out, in formulating a policy to specifically recommend colorectal cancer screening to individuals who infrequently visit medical institutions, we believe it is necessary to address the barriers to screening acceptance and issues of access to healthcare facilities.

In the Discussion part, we changed the sentence from

"Hence, a policy that encourages cancer screening in individuals without periodical hospital visits for comorbidities is crucial."

To

"Hence, it would be beneficial to develop policies that specifically encourage cancer screening for those who do not regularly visit the hospital due to comorbidities, considering the barriers to acceptance of screening and the causes of lack of access to healthcare facilities in this population."

2. Comments from Editorial Office

LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

And

EDITORIAL OFFICE'S COMMENTS; Language evaluation:

The English-language grammatical presentation needs to be improved to a certain extent. There are many errors in grammar and format, throughout the entire manuscript. Before final acceptance, the authors must provide the English Language Certificate issued by a professional English language editing company.

Response: Thank you for your comments. As non-native English speakers, we have submitted our revised manuscript to an English language editing company for grammatical corrections and have attached the certificate of English proofreading.

3. Comments from Editorial Office

Table(s) and figure(s): There are 1 Figure and 5 Tables should be improved. Detailed suggestions for each are listed in the specific comments section.

Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. With respect to the reference to the Figure, please verify if it is an original image created for the manuscript, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed. All legends are incorrectly formatted and require a general title and explanation for each figure. Such as Figure 1 title. A: ; B: ; C: .

Response: Thank you for your valuable feedback. We will submit the Figure in a PPT file. We have revised the legend of the Figure to include the following explanation:

Between January 2016 and December 2019, cancer registries listed 2575 colorectal lesions in 2435 patients. Of these, 198 non-epithelial tumors in 194 patients were excluded. From the remaining 2377 lesions, 105 lesions in 101 patients with unknown diagnostic routes were excluded. Further, 66 lesions in 65 patients with unknown stages were excluded. Of the remaining 2206 lesions, 123 lesions in 113 patients were identified as synchronous colorectal cancers, and after excluding early-stage lesions, 2083 lesions in 2083 patients remained.

Furthermore, we changed the title of Table 3, from

“Stage distribution of the diagnosed patients with colorectal cancer according to the UICC TNM 8th edition in two facilities between January 2016 and December 2019 based on the diagnostic routes”

To

“Stage distribution of colorectal cancer by diagnostic route in two hospitals”

Additionally, we changed the title of Table 4, from

“Stage distribution according to diagnostic routes in two hospitals”

To

“Stage distribution according to diagnostic routes at each hospital”

4. Comments from Editorial Office

Please provide the filled conflict-of-interest disclosure form.

Response: Thank you for your comment. We will submit the conflict-of-interest (COI) disclosure form.

5. Comments from Editorial Office

Please provide all fund documents [Foundation for Cancer Research supported by Kyoto Preventive Medical Center and the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid KAKENHI (JP 22K21080)].

Response: Thank you for your comment. We have scanned and submitted the documents proving the grants received from both institutions.

6. Comments from Editorial Office

The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text (and directly before the References).

Response: We greatly appreciate your valuable suggestions. We have added the "Article Highlights" section at the end of the main text, just before the References, as follows:

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) screening reduces CRC mortality, yet several patients remain unscreened.

Research motivation

Although identifying specific subgroups at high risk is crucial to encourage more individuals to participate in screening, the association between the diagnostic routes and identification of these subgroups has been less appreciated.

Research objectives

This study aimed to determine the stage at diagnosis of CRC based on various diagnostic routes.

Research methods

A retrospective observational study was conducted using data from the cancer registry of two hospitals to clarify the stage at diagnosis in three groups: follow-up (patients detected during follow-up for other comorbidities), symptomatic (patients detected following presentation with CRC-related symptoms), and cancer screening.

Research results

In a study of 2083 patients, early-stage CRCs were diagnosed in 57.3% of the follow-up group, 23.9% of the symptomatic group, and 59.5% of the cancer screening group. The symptomatic group had a lower likelihood of early-stage

diagnosis compared to the follow-up group, while the follow-up and cancer screening groups showed similar likelihoods of early-stage diagnosis.

Research conclusions

CRCs detected during hospital visits for comorbidities were diagnosed earlier, similar to cancer screening.

Research perspectives

Encouraging CRC screening in individuals who do not make regular hospital visits for comorbidities could enhance early detection and improve patient prognoses.

7. Comments from Company editor-in-chief

I have reviewed the Peer-Review Report, full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

When revising the manuscript, it is recommended that the author supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply PubMed, or a new tool, the Reference Citation Analysis (RCA), of which data source is PubMed. RCA is a unique artificial intelligence system for citation index evaluation of medical science and life science literature. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>, or visit PubMed

at: <https://pubmed.ncbi.nlm.nih.gov/>.

Response: Thank you for your comments. We appreciate the conditional acceptance of our manuscript. We have revised the manuscript and, in doing so, have reviewed both PubMed and the Reference Citation Analysis (RCA).

8. About uploading-Signed Informed Consent Form(s) or Document(s)

I am writing in response to the "STEPS FOR SUBMITTING THE REVISED MANUSCRIPT" section, particularly regarding Step 7: Upload the Revision files, where "signed informed consent forms or documents" are listed as a requirement.

In the case of our study, as detailed in our manuscript, we employed a methodology where "Anonymized data were used in this study. The board approved an opt-out approach for the research use of the data. Information about the study's purpose and data usage was posted on the hospital's website rather than obtaining patient informed consent, ensuring patients' right to withdraw."

Consequently, we do not possess any signed Informed Consent forms or Documents.

Therefore, in compliance with these guidelines and to provide the necessary information, we have attached the relevant document that is published on the hospital's website.