



## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 88770

**Title:** T2WI-based radiomic-clinical machine learning model for predicting the differentiation of colorectal adenocarcinoma

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03552126

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor

**Reviewer's Country/Territory:** Hungary

**Author's Country/Territory:** China

**Manuscript submission date:** 2023-10-09

**Reviewer chosen by:** Jia-Ru Fan

**Reviewer accepted review:** 2023-11-23 07:57

**Reviewer performed review:** 2023-12-04 23:42

**Review time:** 11 Days and 15 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

Dear Authors, I have read your manuscript with interest. In the age of AI of course your approach is valid and worthy. I would ask, how you could involve your method into clinical usage/practice to help the routine work. As you described MR is a very good imaging tool for making the TNM for CRC. How could you add some more information to clinical decisions with your method? As MRI seems to be a reliable method, I think a complete TNM and other markers (not only grade, but MSI, LVI can be also assessed by MRI. I would appreciate some comments/discussions about it. I listed some questions/comments below, please answer them and correct the manuscript according to these I would rather use grade than degree for differentiation. Lines 11-13: why imperativus? Please correct for complete sentences. Histology grade is sometimes used as a three or four tiered classification, but you used the two-tiered, which is preferable since it is more reliable so I agree with it. Though, sometimes you still mention well and moderately differentiated tumors. Please follow the two-tiered classification throughout the whole manuscript. Furthermore, there are some other factors which define grade: mucinous cancers, medullary type etc. Did you incorporate these kind of CRCs, too? We



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usually use CRC, CRAC is not used. CRC usually means adenocarcinoma, which is the vast majority of colorectal cancers. I do not think, that grading before surgery could help/change therapeutic decisions, since surgery is usually a must. But of course, any grading would help prognostication. Actually TNM is a very strong prognosticator, which can be also performed with imaging techniques. Furthermore, MSI, tumor budding, LVI, PNI, molecular alterations etc are also very important prognosticators, which features are also examinable with imaging techniques...as you also mentioned. Could you please discuss about these, too? Especially about its AI-ability and of course in radiology setting, so not histological AI! Preoperative grading on biopsy material is not a routine, since tumor heterogeneity can alter biopsy grade, as you correctly mentioned. Please explain all abbreviations upon first mentioning. I did not see A,B and these letters in the Figures. Legends for figures should be comprehensive and self-explanatory, Eg. I saw a nice violin plot graph, but this was not mentioned in the legends. In lines 156-158 you wrote geometric features etc but in figure1 these are called/wrote differently. Please harmonize those... What does circumference and 0,1 mean in Table 1. Tables also need legends with proper descriptions. Please describe all methods you used well understandably. How do you explain the striking difference in performance of your various models? There were several ones with AUC around 1 in training, which proved to be much worse in the validation cohort. There are also a lot of unexplained abbreviations in table 2. Legend is needed. I would list abbreviations in an alphabetical order. There is no need for repeating the DOIs in the reference list.



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**Peer-review model:** Single blind

**Reviewer's code:** 07100515

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Mexico

**Author's Country/Territory:** China

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Novelty of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
<b>Creativity or innovation of this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**SPECIFIC COMMENTS TO AUTHORS**

The article entitled “A T2WI-based radiomics-clinical machine learning model to predict the differentiation of colorectal adenocarcinoma” presents research on the use of machine learning on T2WI images of patients with colorectal adenocarcinoma for the development of models based on radiomics, clinical- radiomics, and clinical features. The generated models were developed and validated to predict the degree of differentiation of colorectal adenocarcinoma, verifying their performance as a tool that favors the histological identification of colorectal adenocarcinoma. Below I pass my judgment on the article and describe my observations: Is this research appropriate for the journal? The article makes an innovative contribution to the diagnosis of colorectal adenocarcinoma through original research. This work presents an advance in the use of machine learning and radiomics tools, demonstrating its potential application in the health area. Furthermore, the manuscript is aligned to the aim and scope of the journal, so it is a contribution that I consider appropriate for the journal. Does the content have archival value? Partially, the manuscript could include a richer comparison and discussion with the existing literature. Despite the innovative and original nature of their



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research with T2WI images, several models based on machine learning have already been reported with other types of MRI. Making use of this background would have a better possibility of contrasting and providing both improvements and limitations of their proposal, improving the archival value of the manuscript. Is this research important to the field? It presents an innovative alternative to improve prediction models and prognosis of colorectal adenocarcinoma in its different degrees of differentiation. It is a relevant proposal in the field, which could represent a high-impact contribution. However, it is necessary to exploit these advantages in the development of the model and its validation so that the manuscript better reflects the strengths of its research. Does the introduction clearly explain motivation? Partially. Although the introduction is clear about the information on adenocarcinoma and its context, more emphasis needs to be given to the role that the different degrees of differentiation play in the prognosis, response to treatment and medical conditions of patients with colorectal adenocarcinoma, so that the need for research development is more evident. Furthermore, the possible scope of using T2WI-derived images and model generation using machine learning remains to be included to fully cover the motivation of the manuscript. Is the manuscript clear and balanced? No. Tracking the different sections of the manuscript makes it difficult to fully track the content. Elements described in one way in Abstract and Methods are usually not completely the same as what is described later in the Discussion, making the content of the article confusing and unbalanced. It is necessary for the authors to carry out an exhaustive review of their manuscript, where they objectively consider whether their ideas described throughout the entire writing remain consistent, because they are not. Is the author a source of new information? Yes, the author could be a source of new information Does the paper stay focused on its subject? Yes, the manuscript stays focused on its subject Are the ideas and methods presented worthwhile, new, or creative? Partially. I have identified little about the use of



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T2WI images and radiomics for the development of models with machine learning, which objectively I consider to have made a contribution to the development and validation of the model. However, other forms of MRI and radiomics have already been used to develop similar machine learning models in other types of cancer. Does the paper evaluate the strengths and limitations of the work described? Partially. The limitations are briefly mentioned in the final part of the Discussion section. However, I could not identify a direct comparison with other models that would allow us to contrast and exploit the advantages that the use of T2WI images could mean in colorectal adenocarcinoma or even other types of cancer. Is the impact of the results clearly stated? No. There is no real discussion of the results obtained in the article. Although the evolution of some processes to obtain the results through the analysis carried out on the data during the generation of the models by machine learning is clear throughout the manuscript, the interpretation, comparison with the bibliography and discussion of these results is very vague or sometimes non-existent. The impact of the research in the field, the possible scope or the relevance in the area is not shown, despite the interesting nature of the research. I believe that it is a research with a lot of potential if the results compared with other models allow us to understand its benefits and perspectives of the application of radiomics as a diagnostic tool. Is the paper free from personalities and bias? Yes, the manuscript is free from personalities and bias. Is the work of others adequately cited? Partially. References are needed to contrast and provide a clear contextualization of the use of radiomics and machine learning models as a background for this work. The comparison and positioning of this manuscript with respect to the existing bibliography is substantial in order to provide a complete judgment regarding its impact on the area. Are the tables and figures clear, relevant, and correct? No. The figures contained in the manuscript lack a good description in the figure caption, in addition to having non-homogeneous formats and styles. The titles of tables and figures are usually too



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generic and not very descriptive. It is necessary that the figures are presented in a clean and clear way, that they have a good appearance and format. Authors should verify the format of the graph axes, be clear in the names of the variables (without using “\_”, and maintain consistency throughout the document in the use of upper and lower case letters. These elements will give greater presentation to the manuscript once this editing process is carried out. Does the author demonstrate knowledge of basic composition skills, including word choice, sentence structure, paragraph development, grammar, punctuation, and spelling? Partially. Although they have a composition that can be understood, sometimes it is not very fluid and confusing. The structure of the paragraphs has to be modified so that there is cohesion in the text of the different sections, since basic sections such as Introduction or Discussion sometimes lose meaning and do not present a specific idea. It is mandatory that the Discussion section have a common thread that complies with fluidity, coherence and cohesion, elements that are lacking in this version of the manuscript. (1) Is the manuscript important/innovative and why? The article is relevant in the area because it proposes a novel strategy for predicting the degree of differentiation of colorectal adenocarcinoma using T2W1 images and machine learning. It proposes an innovative alternative based on radiomics that could be of high impact for the journal. In particular, does it contain new concepts, hypotheses, and/or mechanistic, diagnostic or therapeutic information, or does it represent a state-of-the-art review of the topic?; In particular, the manuscript develops a model based on clinical-radiomics features that provide originality and innovation to the research. It also proposes the use of radiomics and machine learning with the use of T2WI images, which has been little explored for these purposes in this type of cancer. and (2) Is the manuscript well, concisely, and coherently organized and presented? No. The article is not organized coherently. There is no clear thread between sections and there are often discrepancies between them. 1 Title. Does the title reflect the main



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subject/hypothesis of the manuscript? Partially, the title accurately reflects only part of the main subject of the manuscript. The authors developed three different models with the use of clinical characteristics and/or radiomics through machine learning, so I would recommend that the title reflect this in plural. 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? No. The complete manuscript differs greatly from what is described in the Abstract section, it seems that only fragments of the methodology were included, so it differs from what is described in its results. I consider that of all the sections, this is the one that least reflects the research carried out. 3 Key Words. Do the key words reflect the focus of the manuscript? Forks. Some keywords seem to be somewhat repetitive, but in general if the order is changed they do reflect the focus of the manuscript. 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Regarding the background and status, yes, the manuscript describes it adequately. On the other hand, when it comes to the significance, impact, and necessity of the study, the manuscript falls very short. It is necessary to provide complete perspectives on the use of Radiomics in Machine Learning models, as well as clearly describe the selection of T2WI, so that the approach of this research is clearer. 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes, although it is not entirely clear. It is necessary to rethink how it is being described and correctly differentiate between models based on radiomics, clinical-radiomics, and clinical features. Additionally, I recommend verifying that LASSO analysis and feature selection are fully described. Additionally, it is necessary to include a section with a detailed description of the features necessary to obtain T2WI images that are useful to avoid their subsequent exclusion from this type of studies. 6 Results. Are the research objectives achieved by the experiments used in this study? Yes, the described objectives were achieved in the manuscript. What are the contributions that the study has made for



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research progress in this field? The inclusion of T2WI images and radiomics in machine learning models for the prediction of the degree of differentiation of colorectal adenocarcinoma. 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly, and logically? Partially. The manuscript describes good performance of the models predicting the degree of differentiation of colorectal adenocarcinoma. However, although the models have remarkable performance, it is not excellent. The Discussion section needs to logically reflect the discussion thread, since they are disconnected paragraphs. Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Partially. The applicability and relevance is not discussed efficiently with the work of other authors. Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? No, the Discussion section lacks a common thread. The paragraphs seem to have no cohesion and it is necessary to really compare them with the bibliography of other models, proposing the advantages and limitations against other authors. 8 Illustrations and tables. Are the figures, diagrams, and tables sufficient, good quality and appropriately illustrative, with labeling of figures using arrows, asterisks, etc, and are the legends adequate and accurately reflective of the images/illustrations shown? No. The figures lack formatting and the figure caption is vague or does not reflect a clear description of the figure. The figures are not of good quality, editing is needed so that they have a format that corresponds to a publication in an international journal. 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Yes. However, I recommend that all statistical tests, including LASSO analysis and feature selection, be verified. 10 Units. Does the manuscript meet the requirements of use of SI units? Due to the nature of the research, the use of SI units does not apply. 11 References. Does the manuscript appropriately cite the latest, important and authoritative references in the Introduction and Discussion



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sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? There are some references where there should not be any and bibliographic support needs to be included in some elements of the text. 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? No. The manuscript does not present coherence between sections and usually does not have cohesion between some of its paragraphs (mainly in the Discussion section). Is the style, language and grammar accurate and appropriate? No. Sometimes it is confusing and unclear. I recommend restructuring and considering greater cohesion between your paragraphs and sections. 13 Research methods and reporting. Authors should have prepared their manuscripts according to BPG's standards for manuscript type and the appropriate topically-relevant category, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. For (6) Letters to the Editor, the author(s) should have prepared the manuscript according to the appropriate research methods and reporting. Letters to the Editor will be critically evaluated and only letters with new important original or complementary information should be considered for publication. A Letter to the Editor that only recapitulates information published in the article(s) and states that more studies are needed is not acceptable? The manuscript is prepared according to the standards. 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? It's not entirely clear. The authors presented a document that, although signed and sealed, is in Chinese. I recommend that



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a transcript certified by a translator be generated, which guarantees the content of the document regarding the ethical committee. First, what are the original findings of this manuscript? That it is possible to generate and validate a T2WI model based on machine learning to predict the degree of differentiation of colorectal adenocarcinoma. What are the new hypotheses that this study proposed? It is possible to develop and validate models based on machine learning with radiomics features of T2WI images to predict the degree of differentiation of colorectal adenocarcinoma. What are the new phenomena that were found through experiments in this study? The most significant clinical and radiomics features for the development of radiomics, clinical-radiomics, and clinical models of T2WI images using machine learning. What are the hypotheses that were confirmed through experiments in this study? The applicability of radiomics and machine learning on T2WI images for the discrimination of the degree of differentiation of colorectal adenocarcinoma. Second, what are the quality and importance of this manuscript? Although the article is innovative and could have a good impact, the quality of the manuscript is not very good. What is needed is a real discussion of the data, a detailed and consistent description of the methodological process. The article lacks consistency and cohesion between sections, so the quality of the content could be better. What are the new findings of this study? The applicability of radiomics on T2WI to discriminate between differentiation grades of colorectal adenocarcinoma. What are the new concepts that this study proposes? The manuscript does not propose a new concept, only a variant application of machine learning and radiomics in colorectal adenocarcinoma. What are the new methods that this study proposed? The use of clinical-radiomics features for the development of a machine learning model with T2WI images. Do the conclusions appropriately summarize the data that this study provided? Partially, since I consider that it surpasses the aspects developed with this research. What are the unique insights that this study presented? Prediction of the degree of



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differentiation of colorectal adenocarcinoma with a machine learning model based on T2WI images and radiomics. What are the key problems in this field that this study has solved? The difficult identification of the degree of differentiation of colon adenocarcinoma with naked-eye T2WI images by the health specialist. Therefore, the use of radiomics could improve the degree of prediction, favoring the specialist to have more tools in the histological identification of this condition. Third, what are the limitations of the study and its findings? The variability of T2WI images between hospitals, which makes even more evident the need to include a section in the methodology of the features necessary for image acquisition. In this way, the inclusion of more patients and hospitals would be improved, making these models more robust and improving their applicability in the health area. What are the future directions of the topic described in this manuscript? Continue to explore the applicability of radiomics in the diagnostic and differential area through the use of MRI imaging. What are the questions/issues that remain to be solved? It is not clear in the manuscript. What are the questions that this study prompts for the authors to do next? It is not clear in the manuscript. How might this publication impact basic science and/or clinical practice? The research proposed in this article can have a high impact on the development of prediction models for histological differentiation in cancer by applying radiomics and machine learning to images obtained by MRI. The manuscript could impact future applications of radiomics in the differential diagnosis of diseases and the clinical practice of health specialists to encourage the use of this type of models as a tool for the development of personalized treatment.