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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 67219

Title: Can the CT texture analysis of colorectal liver metastases predict the response to first-line cytotoxic chemotherapy?

Reviewer's code: 05625827
Position: Peer Reviewer
Academic degree: FASCRS, MD, PhD
Professional title: Lecturer
Reviewer's Country/Territory: Japan
Author's Country/Territory: Italy

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
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SPECIFIC COMMENTS TO AUTHORS

This manuscript presents the predictive CT texture of responding CRLMs. This study is important for understanding imaging biomarker with CT texture analysis. However, the impact is lost by exclusion of patients treated with chemotherapy combined with targeted therapy. Major points: 1. As stated in the introduction, there has been an increase in the PFS and OS rates since the introduction of targeted therapies. Standard first-line regimen for patients with metastatic colorectal cancer is doublet or triplet chemotherapy combined with a molecular targeted drug. You should mention why the authors focused on the chemotherapy without targeted therapies. 2. Several studies about CT texture analysis for predicting the response to chemotherapy for CRLMs has been done. I think you need to clearly articulate why this study has to identify other new imaging biomarkers. The authors would say what is the lack in the previous studies in the introduction section in detail. 3. The discussion section seems rather abrupt and muddled. The arguments should be laid out clearly based on your results.

We thank you for your constructive observations and questions. Please find the responses to your questions below:

1. Unfortunately, the oncology patients in our geographic area are often limited by the number of follow-up CT scans and chemotherapy regimes which are permitted by their medical aid / funder plans.
    a. The cost of targeted therapy is high and most of our patients cannot afford the expensive targeted therapy due to limited medical funder benefits. Please note from the patient selection flow chart that only 12 of 236 patients (5%) received targeted therapy (Bevacizumab (Avastin) or Cetuximab) as first-line therapy for

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the period March 2012 to May 2020. One of our oncologists recently indicated that about 30% of our patients currently receive combined targeted therapy as first-line treatment in metastatic colorectal cancer.

b. Due to limited medical funder benefits our oncologists occasionally assess the response to chemotherapy clinically and in some patients a follow-up CT scan is only performed when clinical disease progression is suspected. Our oncologists have indicated that it will be advantageous if we as radiologists could identify texture features on the baseline CT scan which could predict and estimate the response to chemotherapy in order for those patients to be more closely monitored and scanned earlier to determine whether the chemotherapy regime should be adjusted. This is the reason we focused on only cytotoxic chemotherapy in our study. If the oncologists knew that the cytotoxic chemotherapy would be ineffective they could promote the use of targeted therapy sooner (personalised medicine).

c. A follow-up study should definitely focus on the combination of cytotoxic and targeted therapy to determine if any other texture analysis features are significantly associated with response in combined therapy.

2. New biomarkers and comparison with previous studies:

a. Only two previous studies focused on the prediction of therapy response in patients who only received FOLFOX or FOLFIRI by means of CT texture analysis. In both studies only first order (histogram) texture features and a few limited GLCM features were assessed. We assessed additional first and second order texture features in our study and identified other predictive first and second order texture features which were associated with therapeutic response. All these texture features were not evaluated in other studies.

b. Our study is also unique since only non-calcifying and non-necrotic colorectal

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liver metastases (CLRM) were evaluated. None of the other studies clearly excluded necrotic or calcifying CRLMs.

c. We limited the imaging variables in our study as far as possible to enable accurate texture analysis. All the scans were performed on GE 16 slice CT scanners with 1.25 mm reconstructions (and 1 x 1 mm trilinear repolarization for texture analysis).

d. In previous studies the slice thickness varied between 2 mm and 5 mm which introduces partial volume effects which will influence the texture analysis results. Furthermore, in some studies the adherence with the image Biomarker Standardization Initiative (IBSI) was not clearly stated.

3. We have edited the manuscript (introduction and discussion) according to your suggestions.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 67219

Title: Can the CT texture analysis of colorectal liver metastases predict the response to first-line cytotoxic chemotherapy?

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
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SPECIFIC COMMENTS TO AUTHORS

1.As we all know, the PFS of first-line chemotherapy is 5-6 months. More than 7 months delay since onset of first line chemotherapy and follow-up CT scans may affect the response evaluation. So, is it appropriate to include the patients that the interval of CT scan was less than or equal to 7 months since onset of first line chemotherapy in "METHODS"? 2. Considering the heterogeneity of tumor, according to RECIST 1.1 standard, only two liver metastases can be selected as target lesions, and other lesions can only be regarded as non-target lesions. And the evaluation criteria for these two types of lesions are different. But the study did not indicate whether both types of lesions were included in the analysis. 3. There is an error in "Table 3 RECIST RESPONSE"; PD is wrongly expressed as PR.

We thank you for your constructive questions regarding our manuscript. Please find the responses to your questions below:

1. Follow-up regime first-line chemotherapy:
    a. In our study we did not focus on PFS or Overall Survival (OS) as was outlined in our manuscript.
    b. Our study's main focus was to determine if we could identify biomarkers which could predict the response of CRLMs to first-line chemotherapy and the RECIST 1.1 criteria was the standard of reference. Many radiomics studies are currently attempting to identify predictive biomarkers in various cancers. Our oncologists do follow-up CT scans every 2-3 months after the onset of first-line chemotherapy (where possible) to determine if there is any therapy response according to the RECIST 1.1 criteria and to determine if the chemotherapy regime should be

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changed. We could identify predictive CT texture features in our study which were associated with therapy response. It will be hugely beneficial to the oncologists if we could identify biomarkers on the baseline imaging examination which can predict the response which can be expected during chemotherapy in order to individualize therapy (precision medicine).

c. Future studies should focus on prognostic texture features which may predict the prognosis, PFS and overall survival (OS).

2. Only a SINGLE TARGET liver metastasis was assessed on the baseline and follow-up examination. No non-target liver metastasis was included in this study.
3. Thank you for pointing out the error on Table 3. This was rectified.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 67219

Title: Can the CT texture analysis of colorectal liver metastases predict the response to first-line cytotoxic chemotherapy?

Reviewer's code: 05775440
Position: Peer Reviewer
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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

Although the results need to be validated with larger patient cohorts, this study found a few texture features and a promising radiomics signature associated with the response of CRLMs to first-line cytotoxic chemotherapy. The heterogeneous conclusion in the field about the texture analysis results associated with responding CRLMs indicate that more study need to improve the prediction of disease. I think this study is contributing to this research field.

We thank you for reviewing our study and for your positive conclusion.

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PEER-REVIEW REPORT

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SPECIFIC COMMENTS TO AUTHORS

The subject of the study is really extremely interesting, current. The effort of the authors in building the work is to be appreciated. At the same time, methodologically, I believe it is impossible to evaluate the correlation of textures with the chemotherapy response considering such different chemotherapy regimens, of such different durations (tissue damage induced by CT is mainly dependent on the type and duration of the CT together with the genetics of the tumor). and other different characteristics, with a sample of only 29 patients. Furthermore, the multivariate analysis should have included all 8 features, but it would have been impossible based on the sample. The sample size is not correct and invalidates the results. Concluding that some features are "significantly" correlated with such a methodology is incorrect.

We thank you for your constructive observations and questions regarding our manuscript. Please find the responses to your questions below:

- We agree that the sample size is not large enough to allow fitting a model with a high number of predictors. Moreover, given the very high correlation between the eight selected variables, it would not be recommended to include them all into the model [Kutner et al. Applied statistical linear models. Mc Graw Hill 2013]. Based on the correlation structure, the eight variables could be classified in two groups: group 1: minimum histogram gradient intensity, discretized intensity skewness, skewness; group 2: long run low grey level emphasis, low grey level count emphasis, low grey level run emphasis, volume at intensity fraction 10%, short run low grey level emphasis. We fitted 15 models, each including one variable from group 1 and one from group 2, and selected the final model based on AUC, sensitivity and specificity. The statistical approach we have adopted is part of standard practice, and the small sample size does not bias the

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estimates but affects their precision, as reflected by the wide confidence intervals of the odds ratios. The need of replicating the results in larger samples has been highlighted in the conclusions.

- The selection of the first-line cytotoxic chemotherapy regimen, the number of chemotherapy cycles administered and the time interval between the baseline and follow-up scans varied in the study cohort as stated above. Unfortunately, this is reflective of the patients that were treated at our regional private oncology practice and we will not be able to rectify this without fragmenting the cohort into smaller groups.
- Although the chemotherapy regime varied, we only included patients on cytotoxic chemotherapy in our study and the additional therapeutic effect of targeted therapy which could have influenced the results was not evaluated.
- Despite the fact that the timing of the follow-up CT scans and duration of chemotherapy varied it is still noteworthy that we could notwithstanding identify texture features which were associated with a response to therapy. Validation of the results in a larger more tightly controlled cohort study is required as recommended in the conclusion of our study.