**Response to Reviewers Post-Revisions**

We thank the reviews again for providing feedback to the manuscript and that the majority of comments in the initial review have been resolved. We are again receptive to the next round of comments and have made changes to the manuscript to address them, following the detailed list of changes below. We look forward to continuing the publication process with phiRO.

Editor Comments

**E1:** change literature citations to year;vol:page-page.

**Author Response:** Citations have been changed to the year;vol:page-page format instead of year;vol(num):page-page (with the page numbers now not truncated if the leading digits are similar)

**Changes to Manuscript:**

Updated citation list to the following format (each citation has been changed, not all citations pasted in the response to reviewers document for brevity):  
  
Old:  
[1] Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio K, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818-27. https://doi.org/10.1097/01.sla.0000128305.90650.71.

New:  
[1] Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio K, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239:818-827. https://doi.org/10.1097/01.sla.0000128305.90650.71.

**E2:** omit using any abbreviations in the highlights section.

**Author Response:** Abbreviations have been removed from the highlights section.

**Changes to Manuscript:**

(2 occurrences) Changed:  
“CT”

To:

“Computed tomography”

**E3:** supplementary material must be submitted as a separate pdf document.

**Author Response:** Supplementary material has been moved to a separate pdf document.

**Changes to Manuscript:**

Removed supplementary material from main manuscript.

Added supplementary material to a new file, supplementary\_material.pdf

**Reviewer A:**

**A1:** The authors have answered all of my questions and have improved the manuscript accordingly.

**Author Response:** We interpret this comment as the reviewer indicating completion of changes from the previous comments.

Changes to Manuscript: None

**Reviewer B**

**B1**: Grey value rounding mentioned in Supplementary Table S2 is something different than what is described. The idea is that because CT is based on Hounsfield Units, a CT image after resampling should consist of integer values as well. The IBSI therefore recommended rounding these values for CT imaging. Rounding generally has a very minor impact on feature values. Moreover, if the nearest neighbour interpolation is used, it is not necessary - resampling in this manner produces integer values.

**Author Response:** We agree with this assessment and recognize that the description in Table S2 is not accurate.

**Changes to Manuscript**

Changed:

|  |  |  |
| --- | --- | --- |
| Gray value rounding | Does not resample to similar resolution if original intensity is lower precision | Resamples to similar resolution if original intensity is lower precision |

To:

|  |  |  |
| --- | --- | --- |
| Gray value rounding | Does not implement resampling of similar resolution to original intensity values, with the argument that differences are likely to be minor and may add complexity. | Resamples to similar resolution of original CT image i.e. rounding to integer resolution of Hounsfield Units from the original CT intensity data. |

**B2:** In addition to reporting the deviations from the IBSI guidelines, it would be useful to report the settings that were used to compute features.

a. To which resolution were images resampled using nearest neighbour interpolation?

b. What method was used to discretise intensities prior to computing texture features. What bin size was used or what number of bins were created?

c. How were texture matrices aggregated? You may want to consult the IBSI reference manual for the different options.

**Author Response:** We have investigation the API of the radiomics software and report on the suggested settings if they were available. In our instantiation of the API, we set the resampler to the default value (resampledPixelSpacing = None), which to our understanding deactivates resampling (https://pyradiomics.readthedocs.io/en/1.2.0/usage.html). For point c), we interpret the Pyradiomics API to provide the ITBB method for texture aggregation in the IBSI documentation by computing a 3D matrix and averaged over the 3D directions (3D as volume, without merging).

**Changes to Manuscript:**

In “Methods”:

Added:  
“Radiomic feature settings were selected used with the Pyradiomics application programming interface. Specifically, resampling was not performed, intensities were discretized with a fixed bin width of 25, and texture matrices were computed by aggregated from averging the 3-dimensional directions from each individual 3-dimensional matrix.”

**B3:** Please describe which and how much contrast agent was used in the imaging protocol? At which point after administration were CT images acquired? This does not need to be exact numbers, but it is important to know if the imaging was obtained in the portal venous phase or at a different time point.

**Author Response:** We have added information regarding the contrast used and acquisition protocol. Specifically, 150mL of iohexol was administered with imaging at the portal venous phase.

**Changes to Manuscript:**

In Results:  
Changed:  
“CT imaging with intravenous contrast”  
To:  
“Images were included if taken under a contrast enhancement protocol where 150mL of intravenous iohexol contrast was administered and images were acquired at the portal venous phase, 75 seconds after the start of injection.”

**B4:** In supplementary table S5, check that all numbers add up to 97 (and 100%). The metastasis and RT characteristics seem to lack a few patients. Also, "Mean time to FFLP" should be "Mean time to local progression".

**Author Response:** Thank you. There was 1 patient that was exported incorrectly from the raw data, leading to missing data in some categories. The table has been reviewed and the missing data points have added to the table to complete the count. All percentages now add up to 100, the discrepancies were a rounding error where not enough significant figures were used. This has been adjusted so that total percentages add up to 100. “mean time to FFLP” has been changed to “Mean time to local progression”

**Changes to Manuscript:**

In supplementary Table S5:  
Changed the following rows:

|  |  |
| --- | --- |
| Metastasis at time of diagnosis, n (%) |  |
| M0 | 31 (32) |
| Other sites at diagnosis, n (%) |  |
| Undetermined | 2 (2.1) |
| RT to other sites, n (%) |  |
| No | 57 (58.8) |
| Other sites at RT, n (%) |  |
| Lung | 21 (21.6) |
| Non-regional LN | 8 (8.2) |
| Freedom from local progression (FFLP), n (%) |  |
| Progression | 50 (51.5) |
| Mean time to FFLP (months) ± SD | 10.5 (8.8) |
| Any hepatic progression (AHP), n (%) |  |
| No progression | 16 (16.5) |

To:

|  |  |
| --- | --- |
| Metastasis at time of diagnosis, n (%) |  |
| M0 | 32 (33) |
| Other sites at diagnosis, n (%) |  |
| Undetermined | 2 (2.0) |
| RT to other sites, n (%) |  |
| No | 58 (59.8) |
| Other sites at RT, n (%) |  |
| Lung | 21 (21.7) |
| Non-regional LN | 8 (8.3) |
| Freedom from local progression (FFLP), n (%) |  |
| Progression | 50 (51.6) |
| Mean time to local progression (months) ± SD | 10.5 (8.8) |
| Any hepatic progression (AHP), n (%) |  |
| No progression | 16 (16.4) |

**B5:** Table 2 should probably be formatted to show all data side by side to make it easier to read.

**Author Response:** We recognize table 2 is very cumbersome. Ideally it would not be concatenated vertically, though we are at the table + figure limit at the moment. If we are interpreting this comment correctly - we have considered making in widthwise with data side by side (i.e. the table with feature selection, without feature selection, with Cox), but am unsure if it is compatible with the width requirements given the font size and document requirements. We have deferred a note to the editor regarding its format that is suitable for the journal and are agreeable to any suggested changes.

**Changes to Manuscript:**

None, but completely open to suggestions to reviewer + editor if suitable to the journal formatting requirements.

**B6:** The authors mention "This may indicate inhomogeneous interactions of electromagnetic radiation with the liver tissue" in the discussion. This is of course correct, but from my perspective does not really help the reader understand what is happening. Also note the interaction of the X-ray beam with the contrast agent. You may be observing (clinically relevant?) differences in local uptake. I would recommend consulting with an (abdominal) radiologist to assess what the feature values could be indicative of. You could also use the model to help explain the role of such features, for example by creating individual conditional expectation plots for FFLP probability at 12 months.

**Author Response:** We recognize the comment is very vague and does not reveal any details of tissue changes i.e. regions with contrast enhancement would systematically create positive skew due to its high attenuation. To our knowledge, there is limited literature studying homogeneity of gray levels within the liver. We have added one citation that has studied radiomics and skewness as well and report on their observations. We have expanded on the thesis of the paragraph – which is that there is limited understanding of what the feature value means but the observation of predictive feature values motivates future studies, such as with histology, to understand association with cellular changes.

**Changes to Manuscript:**

Changed:  
“This may indicate inhomogeneous interactions of electromagnetic radiation with the liver tissue, but the cause of the inhomogeneity is not well understood. Hence, the features determined to be predictive require future studies to understand how they are related to pathophysiology of metastases.”

To:  
“For instance, positive skewness mathematically indicates asymmetric intensity distribution biased for higher intensities. However, the cause of increased skewness is indeterminate. Hypotheses include fresh blood having greater attenuation than denatured blood or high intensity occurring due to greater distribution of contrast, which is expected to be high density [37]. The observation that radiomic features are predictive motivates further studies to associate with structural changes. In future studies, histological analysis comparing regions of different skewness may reveal cellular changes that represent progression of disease.”

With the citation:  
[37] Miles KA, Ganeshan B, Hayball MP. CT texture analysis using the filtration-histogram method: what do the measurements mean?. Cancer Imaging. 2013;13(3):400-406. doi:10.1102/1470-7330.2013.9045

**B7:** Thank you for replacing figure 2. The ROI overlay in the new figure obscures the interesting parts of the scan. Is it possible to only show the boundaries of the ROI? Also, please describe the visualised regions of interest in the figure legend.

**Author Response:** It is certainly possible to show the boundaries of the ROI. A new figure has been uploaded with opacity decreased in the ROI. A figure legend has been added on the image described the regions visualized.

**Changes to Manuscript:**

Changed Figure 2 to:

Graphical user interface, application

Description automatically generated