**Title:**

**Prediction of Local Control for Colorectal Liver Metastases using a Radiomic Artificial Intelligence Model**

Ricky Hu\*1, Ishita Chen\*2, Jacob Peoples3, Jean-Paul Salameh1, Mithat Gönen4, Paul B. Romesser2, Amber L. Simpson3,5, and Marsha Reyngold2

\*Equal Contribution and Co-First Authorship

1School of Medicine, Queen’s University, Kingston, ON

2Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY  
3School of Computing, Queen’s University, Kingston, ON  
4Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

5Department of Biomedical and Molecular Sciences, Queen’s University, Kingston, ON

**Corresponding Author:**

Name: Ricky Hu

Email: rhu@qmed.ca

**Highlights**:

* CT imaging contains quantifiable features to characterize colorectal liver metastases
* We computed shape, statistics, and textural radiomic features to characterize a CT liver volume
* We developed an artificial intelligence model to predict local progression from radiomic features
* Artificial intelligence model able to predict local progression with high accuracy
* Maximum dosage and textural coarseness of liver volume were highest predictivity features

**Funding Statement:**

PBR is supported by a NIH/ NCI Cancer Center Support Grant (P30 CA008748), NIH/ NCI early career development award (K08 CA255574), and NCI R01 CA233888. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Conflict of Interest Statement:**

PBR is a EMD Serono consultant and reports support for travel from Elekta and Philips healthcare and prior research funding from EMD Serono.

**Author Contributions:**

Ishita Chen: Conceptualization, data acquisition, data processing, data analysis, and writing.

Ricky Hu: Methodology, software development, data analysis, visualization, and writing.

Jacob Peoples: Methodology, software development, data analysis, and writing.

Jean-Paul Salameh: Data analysis and writing.

Mithat Gönen: Biostatistical support, data analysis, and writing.

Paul B. Romesser: Supervision, data acquisition, data processing, data analysis, and writing.

Amber Simpson: Supervision, conceptualization, methodology, data analysis, and writing.

Marsha Reyngold: Supervision, data acquisition, data processing, data analysis, and writing.

**Acknowledgements:**

**Abstract:**

**Background:**

Prognostic assessment of relative treatment efficacy of local therapies for colorectal liver metastases (CLM) is essential for guiding patient management. Existing assessment methodologies are based on clinicopathological variables with limited accuracy and generalizability. Computed tomography (CT) contains detailed liver texture information which may be analyzed by artificial intelligence (AI) to provide quantitative prediction of local control capable of modeling nonlinear variable dependencies. We sought to pilot an automated prediction system for local and hepatic progression-free survival of patients treated with RT for CLM using radiomic and clinical features.

**Methods**

A time-dependent AI survival model was built by first extracting 108 radiomic features from patient CT scans and predicting survival with the random survival forest (RSF) machine learning algorithm. Accuracies were measured by the average concordance index (C-index) and integrated Brier score (IBS). This was repeated with different segmentations of the liver scan and with standard radiotherapy clinical variables as input to the RSF. Feature importance scores were computed by comparing perturbation error rates to identify predictive features.

**Results**

The AI radiomics model achieved a C-index of 0.68 (CI: 0.62 – 0.74), greater than previous studies. IBS for all variations of the models were below the 0.25 threshold for random prediction, indicating that a viable signal exists within radiomic analysis. When combined with treatment input data, the model achieved a C-index of 0.73 (CI: 0.64 – 0.82). In this model, the most predictive radiomic feature was gray tone difference matrix strength (feature importance: 1.90 CI: 0.93 – 2.86) and most predictive treatment feature was maximum dose (feature importance: 3.83, CI: 1.05 – 6.62).

**Conclusions**

The AI radiomics model achieves high prediction accuracy for local control and intra-hepatic progression-free survival of CLM treated with RT, providing support that radiomic analysis of CT scans combined with machine learning analysis may aid in clinical decision making that requires prognostic prediction.

**Main Text:**

**Introduction:**

Patients with colorectal cancer develop colorectal liver metastases (CLM) in approximately 50% of cases [1] with 40% recurring within 12-months. Surgery is the standard of care for patients that present with liver-limited resectable CLM, with reported 5-year survival ranging from 28-58% [2]. Non-surgical liver-directed local therapy for CLM, such as thermal ablation, can be effective, but is invasive [3]. External beam radiation therapy (EBRT) has emerged as an alternative, non-invasive approach for localized therapy of CLM in patients who are ineligible for other treatment options. Numerous clinical factors have been shown to influence the local control of CLM associated with EBRT, including dose delivered to the lesion and the size of the lesion [4]. Prognosis of local tumor control is essential to determine appropriate treatment for CLM. The goal of this work was to build a predictive model utilizing quantitative information from radiomic features contained in computed tomography (CT) scans combined with machine learning methods to predict local control outcomes in CLM.

Several models have been published for predicting clinical outcomes in CLM patients. A common approach is utilizing multivariate Cox proportional hazard regression using clinically relevant variables and selecting high hazard ratio variables for a scoring system [5-13]. Fong et al. [6], for instance utilized 7 clinicopathological characteristics, from which they selected 5 variables (node-positive primary, disease-free interval from primary to metastases, number of hepatic tumors, if largest hepatic tumor >5cm, and if carcinoembryonic antigen level > 200ng/ml) for their scoring system. Wang et al. [14] evaluated the accuracy of 9 different survival prediction scoring systems with the majority of these scoring system resulting in a concordance index (C-index) crossing below the 0.50 threshold in its 95% confidence interval.

There are limitations with these scoring systems, namely that Cox-regression may not capture nonlinear relationships between clincopathological variables, that scoring systems require manual thresholding, and that other data, such as CT imaging, may provide features that can be utilized for outcome prediction. We aim to address these gaps by building a survival prediction model from two motivating ideas: the usage of CT radiomic imaging data and modelling time-dependent survival with machine learning.

CT has been standard of care for characterizing tumor response and radiomics is an emerging field that shows promise in analyzing complex details in CT scans. Radiomic features are computed textural attributes of which quantitatively characterize shape, intensity statistics, and gray-level relationships within the anatomy of interest. Ganeshan et al. [15] observed that intensity and entropy of a liver CT volume of CLM patients significantly changed after contrast injection, indicating that radiomics can capture textural changes from enhancement. Miles et al. [16] investigated radiomics in relation to CLM survival by computing intensity and uniformity features from a CT liver volume and observing that textural uniformity was significantly associated with increased survival. Creasy et al. [17] and Simpson et al. [18] also observed that increased homogeneity in liver CT volumes were associated with increased risk of hepatic recurrence.

Artificial intelligence (AI) methods have shown potential in survival prediction in previous studies [19, 20]. A strength of AI, specifically machine learning, is an automated and iterative approach, where model parameters are repeatedly optimized. This allows for the initialization of complex model architecture which may be more suitable to model interdependent variables than a linear models used for previous scoring systems.

We set out to evaluate whether an automated prediction system can predict progression-free survival for liver metastasis patients treated with RT. To do this, we developed software for the automated extraction of radiomic features from CT liver scans, a machine learning prediction model to utilize radiomic features to predict survival, and the validation of the performance of the model when enhancing radiomic features with clinical data.

**Materials and Methods**

**Data Collection and Equipment:**

This retrospective analysis was approved by the institutional review board with a waiver of informed consent at Memorial Sloan Kettering Cancer Center (MSK) (New York, NY). The MSK database was queried to obtain pre-treatment CT scans data for patients receiving radiation treatment for CLM between February 2006 to February 2019. Liver and tumor volumes were segmented by radiation oncologists at MSK, as part of standard of care. The MSK database was also queried to obtain dosimetric treatment parameters and right-censored time-to-event data for two outcomes: progression anywhere in the liver (any hepatic progression) and progression in the treated tumor (local progression).

**Image Analysis**

The task for the AI model was to predict the primary endpoint, defined as time until local tumor progression. To accomplish this, an AI survival prediction model, visualized in Figure 1, was developed, consisting of an offline training component and a real-time prediction component. The input to the training component is a set of liver CT scans. Radiomic features are extracted from the liver and/or tumor volumes and used to train a survival model, which learns to predict a survival time interval for the patients in the training dataset. After the model is trained, new patient CT scans can be used as an input to the finalized model to compute a real-time survival prediction. The training stage contains three main components: radiomic feature extraction, feature selection, and random survival forest modelling. The AI model was programmed in Python, utilizing the PyRadiomics [21] and PySurvival libraries [22]. Concordance indices were programmed in R with the Hmisc library [23].

Diagram, schematic

Description automatically generated

Figure 1: A visualization of the survival prediction system. The system contains two stages. The first is a training stage, where radiomic features are extracted from a set of computed tomography liver scans. Variance inflation factor and hazard ratio ranking is then used to filter out low information yielding features. The remaining features are used to train a random survival forest prediction model. Once the survival model has been built, it can be exported to a real-time prediction environment, where liver scans of new patients can be fed as input to the survival model to obtain a predicted survival for the new patient. In this way, most of the computation required is done beforehand to build the model and prediction can occur in real-time for new patients.

**Radiomic Feature Extraction**

In the first stage, 108 radiomic features were computed for a liver volume extracted from a CT scan. This includes computations related to shape, intensity statistics, gray-level co-occurrence matrices, gray level run-length matrices, gray level dependence matrices, and gray tone difference matrices. A full list of radiomic features is available in the Supporting Table 1. A visualization of radiomic feature extraction is displayed in Figure 2.

Diagram

Description automatically generated with medium confidence

Figure 2: Visualization of radiomic feature extraction. a) A liver volume is extracted from the computed tomography scan and features relating to the intensity statistics, shape, and gray level matrices of the liver volume are computed. b) An example of one such radiomic feature, skewness, from a liver slice. The skewness generated is a local map of skewness for visualization. In the final radiomic computation, one singular value is computed for the entire volume.

**Feature Selection**

Retaining all 108 radiomic features would likely result in overfitting due the dimensionality of the feature space being too large for the sample size [24]. Redundant features were removed using a variance inflation factor threshold of 10 as an indicator of collinearity [25]. We then ranked remaining features using the hazard ratios predicted for each variable in a Cox proportional hazards model [26], removing features until the ratio of features to samples was less than 1:10.

**Random Survival Forest Model**

To predict survival from the filtered feature set, the random survival forest (RSF) algorithm was used [27]. The algorithm creates ensemble decision tree with nodes representing features with a threshold value. The features used and the threshold values are iteratively optimized to maximize the log-rank statistic between two child nodes. The full algorithm is listed in the supplemental information section. A template RSF was instantiated using the PySurvival library [21] and then hyperparameters of number of trees, maximum number of patients for a terminal node, and maximum depth were optimized with a gridsearch algorithm. After optimization, feature importances were computed by the Gini importance score.

**Validation**

A 4 k-fold cross-validation scheme was used to provide multiple estimates of the performance of the model. The dataset is shuffled and partitioned into 4 equal sized subsets. Each is then used as a test data set for a model trained on the union of the remaining 3 subsets, giving 4 separate models trained and evaluated. The concordance index (C-index) integrated Brier score (IBS) were computed as accuracy metrics to evaluate the models in each k-fold. The confidence interval for the C-index was computed using Somers’ Dxy rank correlation [28].

Ablation analysis was performed to investigate the performance of the model when adjustments to individual components were made. First, we defined 9 different feature sets:

1. Non-imaging and non-treatment clinical data: baseline patient variables not related to treatment information or tumor geometry from CT imaging.
2. Treatment clinical data: variables related to treatment parameters, including dosimetric variables.
3. Imaging clinical data: variables related to tumor geometry measure in CT imaging.
4. All clinical data: The union feature sets 1-3.
5. Radiomics: tumor volume: radiomic features computed from the tumor volume only.
6. Radiomics: liver parenchyma: radiomic features computed from the liver parenchyma only.
7. Radiomics: liver parenchyma + tumor: radiomic features computed from the union of the tumor volume and liver parenchyma.
8. Treatment clinical data and radiomics from liver parenchyma + tumor: the union of feature sets 2. And 7.
9. All clinical data and radiomics from liver paraenchyma + tumor: the union of feature sets 4. And 7.

Table 1 displays a list of categorized clinical variables.

|  |  |
| --- | --- |
| **Category** | **Variables** |
| Imaging Clinical Data | Number of lesions at RT  Other sites at RT  Lesion dimension 1  Lesion dimension 2  PTV (cm3) |
| Treatment Clinical Data | Biologically effective dose (Gy)  Minimum dose for PTV (cGy)  Maximum dose (cGy)  Dose for 95% of target volume (% of intended prescribed dose)  Systemic treatment before RT  Lines of chemotherapy  HAIP before RT  Reirradiation  Surgery before RT  Ablation before RT  TARE before RT  Embolization before radiotherapy |
| Other Clinical Data | Primary tumor subsite  Metastasis at diagnosis  Number of liver lesions at diagnosis  Other sites at diagnosis  Liver location  CEA  KRAS mutation |

Abbreviations: RT = radiotherapy, PTV = planning target volume, HAIP = hepatic arterial infusion pump, CEA = carcinoembryonic antigen, KRAS = Kirsten rat sarcoma virus, TARE = transarterial radioembolization

Table 1: The categorization of clinical variables to imaging, treatment, and other (non-imaging and non-treatment) clinical variables. The goal of this categorization was to observe if different subsets of clinical data performed better at prediction progression in the absence of other subsets.

Each feature set was used to build a RSF survival model. The goal was to evaluate the performance of radiomics compared to clinical data, whether the combination of both enhance performance, whether different radiomic volumes are more predictive, and whether the lack of feature selection will result in overfitting.

**Results**

The query resulted in obtaining imaging and chart data for N=97 patients, with 129 lesions identified on imaging. f the 129 lesions, 55 resulted in local progression, 67 in no local progression, and 7 in undetermined progression. The baseline distribution of clinical variables is summarized in Supporting Table 1. The mean freedom from local progression was 10.5 months. The averaged cross-validation accuracies for different subsets are summarized in Table 2. Samples of the predicted survival and IBS curves compared to the ground truth are visualized in Figure 3. The results of feature importance computation are summarized in Tables 4-6.

|  |  |  |
| --- | --- | --- |
| **Input Features** | **Concordance Index (95% CI)** | **Integrated Brier Score (95% CI)** |
| **(No Feature Selection, Local Progression as Outcome)** | | |
| Other Clinical Data | 0.64 [0.54, 0.75] | 0.18 [0.15, 0.22] |
| Imaging Clinical Data | 0.66 [0.61, 0.71] | 0.17 [0.14, 0.20] |
| Treatment Clinical Data | 0.69 [0.62, 0.77] | 0.17 [0.14, 0.20] |
| All Clinical Data | 0.67 [0.58, 0.75] | 0.16 [0.15, 0.18] |
| Radiomics: Tumor Volume | 0.64 [0.52, 0.76] | 0.18 [0.17, 0.18] |
| Radiomics: Liver Parenchyma | 0.61 [0.53, 0.69] | 0.21 [0.19, 0.23] |
| Radiomics: Liver Parenchyma + Tumor | 0.66 [0.58, 0.74] | 0.2 [0.17, 0.22] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.66 [0.59, 0.73] | 0.19 [0.18, 0.21] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.64 [0.60, 0.68] | 0.19 [0.16, 0.22] |
| **(With Feature Selection, Local Progression as Outcome)** | | |
| Other Clinical Data | 0.66 [0.56, 0.76] | 0.19 [0.16, 0.22] |
| Imaging Clinical Data | 0.61 [0.56, 0.66] | 0.17 [0.14, 0.19] |
| Treatment Clinical Data | 0.72 [0.64, 0.79] | 0.18 [0.15, 0.21] |
| All Clinical Data | 0.62 [0.56, 0.69] | 0.19 [0.16, 0.22] |
| Radiomics: Tumor Volume | 0.68 [0.51, 0.84] | 0.19 [0.16, 0.24] |
| Radiomics: Liver Parenchyma | 0.66 [0.60, 0.72] | 0.20 [0.18, 0.22] |
| Radiomics: Liver Parenchyma + Tumor | 0.68 [0.62, 0.74] | 0.20 [0.16, 0.25] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.73 [0.64, 0.82] | 0.18 [0.15, 0.20] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.69 [0.65, 0.74] | 0.23 [0.21, 0.26] |

Table 2: A summary of accuracy results for each input combination to the model with the standard deviation range. The combination that achieved the highest accuracy was using radiomic features from the entire liver and tumor volume. The variances for the models decreased after feature selection. However, there is still overlap within the confidence intervals of the accuracies.

Nearly all input dataset variations resulted in a C-index greater than 0.50 within 95% confidence interval ranges. The highest local progression prediction accuracy occurred when combining both radiomics of the liver parenchyma and tumor volume with treatment data (C-index: 0.73 [0.64, 0.82]). Utilizing only radiomic data from the liver parenchyma and tumor volume resulted in a C-index of 0.68 [0.62, 0.74]. The IBS of all models were below 0.25, indicating nonrandom prediction [29].

Graphical user interface, chart, application

Description automatically generated

Figure 3: Comparison of the predicted local progression-free survival (red), defined as freedom from local progression, from the random survival forest compared to the actual survival (red) from a Kaplan-Meier model of the outcome data. Comparisons include the best k-fold (left) and worst k-fold (right) during cross-validation from using radiomics using liver and tumor volumes and treatment data (top), radiomics data only (middle), or treatment data only (bottom). All models achieved a higher C-index than models from previously published studies and the usage of radiomic features enhances the accuracy of the model compared to with treatment data alone.

|  |  |
| --- | --- |
| **Feature (Treatment Data Only)** | **Importance Score (95% CI)** |
| Maximum Dose | 10.84 [6.35, 15.34] |
| Carcinoembryonic Antigen at Radiotherapy | 2.69 [-0.43, 5.81] |
| Lines of Chemotherapy | 2.53 [1.16, 3.9] |
| Pump Before Radiotherapy | -0.81 [-1.57, -0.05] |
| **Feature (Radiomics on Liver Plus Tumor Volume Only)** | |
| Neighborhood Gray Tone Difference Matrix Strength | 3.74 [2.25, 5.22] |
| Neighborhood Gray Tone Difference Matrix Busyness | 3.32 [2.5, 4.15] |
| Kurtosis | 1.97 [1.58, 2.37] |
| Maximum 2D Diameter Slice | 1.45 [0.20, 2.69] |
| Gray Level Size Zone Matrix Low Gray Level Emphasis | 0.33 [-0.75, 1.42] |
| Neighborhood Gray Tone Difference Matrix Contrast | 0.02 [-0.78, 0.82] |
| Skewness | -0.25 [-0.81, 0.31] |
| Gray Level Co-occurrence Matrix Cluster Shade | -0.88 [-2.78, 1.01] |
| **Feature (Treatment Data and Radiomics on Liver Plus Tumor Volume)** | |
| Maximum Dose | 3.83 [1.05, 6.62] |
| Neighborhood Gray Tone Difference Matrix Strength | 1.90 [0.93, 2.86] |
| Lines of Chemotherapy | 1.36 [0.38, 2.35] |
| Gray Level Size Zone Matrix Low Gray Level Emphasis | 1.01 [-0.37, 2.39] |
| KRAS Mutation | 0.65 [0.10, 1.19] |
| Carcinoembryonic Antigen at Radiotherapy | 0.48 [-1.11, 2.08] |
| Gray Level Size Zone Matrix Nonuniformity | 0.48 [-0.32, 1.27] |
| Gray Level Co-occurrence Matrix Cluster Shade | 0.17 [-0.98, 1.32] |
| Pump Before Radiotherapy | -0.08 [-1.21, 1.04] |
| Skewness | -0.29 [-0.73, 0.15] |

Table 4: The feature importances for the random survival forest model utilizing treatment data only, radiomics data only, or the combination of both. Maximum dose was observed to be the most predictive feature, significantly with more information gain than any other treatment feature. Gray tone difference matrix computations yielded the most predictive radiomic features when only using radiomics data. Both graytone difference matrices and maximum dose features resulted in high predictive value in the combined model. However, the importance of maximum dose was decreased compared to when using only treatment data, indicating that the model is still able to predict survival with the remaining radiomic features.

The most predictive radiomic feature was the neighboring gray tone difference matrix (NGTDM) strength, though with a large variance over the 4 k-folds. The most predictive clinical variable was maximum dose, significantly greater than any other clinical variable. However, in the combined radiomics and treatment data model, the feature importance of maximum dose decreased.

**Discussion**

The goal of the study was to develop a method utilizing radiomics and machine learning to predict time until local progression of CLM patients. The IBS of every dataset combination was below the threshold of 0.25, indicating that the predictions by the RSF model is non-random and information-gaining [29].

Without feature selection, although the model performed with an average C-index greater than 0.55, there was a larger variance across the cross-validation folds. This is likely due to overfitting as the number of input variables (e.g. all 108 radiomic features vs. a maximum of 9 when feature selected) defines the number of dimensions in the optimization problem for the machine learning model. The optimized solution may be too specific to the training data, resulting in lower testing accuracy.

There are several opportunities we aimed to address to improve on existing methods. First, the Cox regression models data with an exponential hazard function with variables parameterized in a linear combination [30]. This may not sufficiently characterize nonlinear dependencies between the variables. Secondly, the existing studies use Cox regression to extract significant variables and use a manual scoring system to map the variables to a risk category. The linear mapping of hazard ratios to prediction may further oversimplify nonlinear dependencies between variables, particularly when relying on integer scores as the optimal threshold may not be exactly at an integer value. Thirdly, there may be predictive information missed if only analyzing clinicopathological variables. As tumor progression results in changes in tissue, there may be observable structural changes in the liver associated with survival.

Most prior studies reported a C-index lower than 0.60 when tested on external datasets, with one model by Wang et al. achieving a C-index of 0.64 [14]. However, we did not have access to all variables used, which is required for a fairer comparison between manual scoring systems and automated RSF methods in future studies.

The best performing radiomic model was from the union of the liver parenchyma and tumor with feature selection enabled, achieving a C-index (95% CI) of 0.68 (0.62 – 0.74). The radiomic model utilizing the tumor volume only or liver parenchyma only performed within the same confidence interval range as well. This suggests that both the liver parenchyma and tumor contain textural features predictive of local control. As the radiomic features are computed as a single point-data value for the volume, it is difficult to localize the exact regions of abnormal texture. Thus, the features detected indicate an aggregate textural characteristic that contains distinctive information to differentiate local control. Future studies that isolate patches of the liver can be conducted to localize regions with abnormal radiomic values.

An RSF model trained from treatment data resulted in a C-index (95% CI) of 0.72 (0.64 – 0.79). When combining both treatment and radiomic data, the accuracy is retained, with a C-index (95% CI) of 0.73 (0.64, 0.82). In the combined mode, the two most predictive features were similarly maximum dose with a feature importance score (95% CI) of 3.83 (1.05 – 6.62) and NGTDM strength with a feature importance score (95% CI) of 1.90 (0.93 – 2.86). Moreover, the feature importance (95% CI) of maximum dose decreased from 10.84 (6.35, 15.34) in the treatment data only model to 3.83 (1.05, 6.62) in the combined model, indicating that the radiomic features contribute to prediction even when treatment data is available. There are variables similar to maximum dose, such as dose covering 95% of the planning target volume, that are likely predictive but were removed by the feature selection algorithm due to collinearity. It should be noted that dosage is increased for tumors that may have shown radioresistance, hence some expert prior knowledge is required for this variable whereas the radiomic features are dependent only on the image.

The high performance of radiomics model suggests that there is predictive textural information within the liver parenchyma and tumor volume that may be investigated further to understand structural changes that affect prognosis. This is consistent with Simpson et al. [16], who observed that certain radiomic features were associated with recurrence and are then potentially reflective of tissue abnormalities that create a metastatic or protective environment.

There are two major implications of this work. First, radiomic features potentially provide predictive information related to tumor progression. Changes in liver texture visualized on a CT image can be quantified with features associated with progression. Although subjective labelling results in inter-observer error in segmentation of the volume of interest, the extraction radiomic features is quantitative and automated compared to manual analysis of texture, reducing variability. The regions of interest can be analyzed in future studies, such as with histological analysis, to investigate what changes have occurred in the liver that affect local control. For instance, kurtosis measures the weight of the tails in a distribution and if kurtosis is a predictive feature, there may be structural changes associated with local control when a liver has extreme hyperintense and hypointense regions. The second major implication is machine learning methods such as an RSF model can perform prediction tasks that have been historically difficult with linear and manual scoring methods. This supports the potential for machine learning to be used in the future to aid clinical decision making.

**Limitations**

A limitation of the study is the sample size. Despite the observe accuracy of the model, further validation with a diverse patient population from different centers for instance is required to evaluate the generalizability of the model. A wide uncertainty in C-indices indicates that the model accuracy varies for different patients, potentially due to limited training data. In our study, we limited cross-validation to 4 k-folds. With more samples, 5 k-fold or 10 k-fold cross validation, may be conducted to have more testing sets so that accuracy evaluation has more statistical power. Feature selection may be unnecessary with sufficient samples as a random forest can in theory filter variables that have low predictive information gain [31] given enough data. Future studies may include patients before and after radiotherapy, as texture in CT scans may change after treatment.

Although radiomic features may be predictive, we are limited in the clinical interpretation of the features. For instance, high skewness indicates that the intensities in the region of interest are not symmetrically distributed. 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.

**Conclusion**

We have developed a time-dependent tumor progression prediction model for CRM treated with RT utilizing radiomic features from CT scans and an AI random survival forest. The model was able to achieve C-indices greater than previous studies utilizing radiomic features from the liver parenchyma and tumor volume or with treatment data. The resulting model may be applied in future studies to aid in prognostic decision making. Radiomic features determined to be predictive may be investigated in the future to understand structural changes reflected in radiomic observations in the CT scan to provide new directions for clinician analysis of liver texture.

**References:**

[1] Abdalla, Eddie K., et al. "Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases." *Annals of surgery* 239.6 (2004): 818.

[2] Leung U, Gönen M, Allen PJ, Kingham TP, DeMatteo RP, Jarnagin WR, D'Angelica MI. Colorectal Cancer Liver Metastases and Concurrent Extrahepatic Disease Treated With Resection. *Ann Surg*. 2017;265:158–165.

[3] Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 2017.

[4] Mahadevan A, Blanck O, Lanciano R, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. *Radiat Oncol*. 2018;13(1):26. Published 2018 Feb 13. doi:10.1186/s13014-018-0969-2

[5] Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. *Cancer*. 1996;77(7):1254-1262.

[6] Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999;230(3):309-321. doi:10.1097/00000658-199909000-00004.

[7] Iwatsuki S, Dvorchik I, Madariaga JR, et al. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg.* 1999;189(3):291-299. doi:10.1016/s1072-7515(99)00089-7.

[8] Konopke R, Kersting S, Distler M, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. *Liver Int*. 2009;29(1):89-102. doi:10.1111/j.1478-3231.2008.01845.x.

[9] Nagashima I, Tadahiro T, Matsua K, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. *J Hepatobiliary Pancreat Surg.* 2004;11(2):79-83.

[10] Imai K, Allard MA, Castro Benitez C, et al. Nomogram for prediction of prognosis in patients with initially unresectable colorectal liver metastases. *Br J Surg*. 2016;103(5):590-599. doi:10.1002/bjs.10073.

[11] Sasaki K, Morioka D, Conci S, et al. The Tumor Burden Score: A New "Metro-ticket" Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors. *Ann Surg.* 2018;267(1):132-141. doi:10.1097/SLA.0000000000002064.

[12] Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg.* 2008;247(1):125-135. doi:10.1097/SLA.0b013e31815aa2c2.

[13] Brudvik KW, Jones RP, Giuliante F, et al. RAS Mutation Clinical Risk Score to Predict Survival After Resection of Colorectal Liver Metastases*. Ann Surg*. 2019;269(1):120-126. doi:10.1097/SLA.0000000000002319.

[14] Wang K, Liu W, Yan XL, Li J, Xing BC. Long-term postoperative survival prediction in patients with colorectal liver metastasis. *Oncotarget*. 2017;8(45):79927-79934. doi:10.18632/oncotarget.20322.

[15] Ganeshan B, Burnand K, Young R, Chatwin C, Miles K. Dynamic contrast-enhanced texture analysis of the liver: initial assessment in colorectal cancer. Invest Radiol. 2011;46(3):160-168. doi:10.1097/RLI.0b013e3181f8e8a2.

[16] Miles KA, Ganeshan B, Griffiths MR, Young RC, Chatwin CR. Colorectal cancer: texture analysis of portal phase hepatic CT images as a potential marker of survival. *Radiology*. 2009;250(2):444-452. doi:10.1148/radiol.2502071879.

[17] Creasy JM, Cunanan KM, Chakraborty J, et al. Differences in Liver Parenchyma are Measurable with CT Radiomics at Initial Colon Resection in Patients that Develop Hepatic Metastases from Stage II/III Colon Cancer. *Ann Surg Oncol.* 2021;28(4):1982-1989. doi:10.1245/s10434-020-09134-w.

[18] Simpson, AL., Doussot, A, Creasy, JM, et al. Computed tomography image texture: a noninvasive prognostic marker of hepatic recurrence after hepatectomy for metastatic colorectal cancer. *Ann Surg Oncol. 2017;24*(9): 2482-2490

[19] Kim DW, Lee S, Kwon S, Nam W, Cha IH, Kim HJ. Deep learning-based survival prediction of oral cancer patients. *Sci Rep*. 2019;9(1):6994. doi:10.1038/s41598-019-43372-7.

[20] Wang W, Liu W. Integration of gene interaction information into a reweighted random survival forest approach for accurate survival prediction and survival biomarker discovery. Sci Rep. 2018;8(1):13202. doi:10.1038/s41598-018-31497-0.

[21] van Griethuysen JJM, Fedorov A, Parmar C, et al. Computational Radiomics System to Decode the Radiographic Phenotype. *Cancer Res*. 2017;77(21):e104-e107. doi:10.1158/0008-5472.CAN-17-0339

[22] Fotso, S. PySurvival: Open source package for survival analysis modeling. 2019. https://square.github.io/pysurvival/

[23] Harrell, FE, Dupont, C. Hmisc: Harrell miscellaneous. R package version 4.6-0. https://cran.r-project.org/web/packages/Hmisc/index.html

[24] Liu R, Gillies DF. Overfitting in linear feature extraction for classification of high-dimensional image data. *Pattern Recognit.* 2016;53(C):73–86. doi:10.1016/j.patcog.2015.11.015.

[25] Salmeron R, Garcıa CB, Garcıa J. Variance Inflation Factor and Condition Number in multiple linear regression. *J Stat Comput Simul*. 2018;88(12):2365-2384. Doi:10.1080/00949655.2018.1463376.

[26] Bourgon R, Gentleman R, Huber W. (2010). Independent filtering increases detection power for high-throughput experiments. *Proceedings of the National Academy of Sciences of the United States of America*, 107(21), 9546–9551. https://doi.org/10.1073/pnas.0914005107.

[27] Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. *Ann Appl Stat*. 2008;2:841–860.

[28] Newson, R. Confidence Intervals for Rank Statistics: Somers’ D and Extensions. *The Stata Journal*. 2006;6(3):309-334.

[29] Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21(1):128-138. doi:10.1097/EDE.0b013e3181c30fb2.

[30] Lin DY, Wei LJ. The robust inference for the cox proportional hazards model. *J Am Stat Assoc*. 1989;84:1074–1078.

[31] Menze BH, Kelm BM, Masuch R, et al. A comparison of random forest and its Gini importance with standard chemometric methods for the feature selection and classification of spectral data. *BMC Bioinformatics*. 2009;10:213. doi:10.1186/1471-2105-10-213.

**Supplemental Information:**

**Baseline Patient Demographics**

|  |  |
| --- | --- |
| **Characteristics** | **All lesions (n=129)** |
| Number of patients/lesions | 97/129 |
| Sex, n (%) |  |
| Male | 83 (64.3) |
| Female | 46 (36.7) |
| Primary tumor subsite, n (%) |  |
| Colon | 104 (80.6) |
| Rectal | 20 (15.6) |
| Undetermined | 5 (3.8) |
| Number of liver lesions at diagnosis, n (%) |  |
| 0 | 5 (3.9) |
| 1 | 25 (19.4) |
| 2 | 9 (7.0) |
| 3-5 | 32 (24.8) |
| > 5 | 53 (41.0) |
| Undetermined | 5 (3.9) |
| Other sites of metastatic disease at diagnosis, n (%) |  |
| None | 101 (78.3) |
| Lung | 12 (9.3) |
| Non-regional LN | 3 (2.3) |
| Lung and non-regional LN | 4 (3.1) |
| Other | 7 (5.4) |
| Undetermined | 2 (1.6) |
| RT to other sites, n (%) |  |
| No | 75 (58.1) |
| Before liver RT | 28 (21.7) |
| After Liver RT | 21 (16.3) |
| Before and after liver RT | 2 (1.6) |
| Undetermined | 3 (2.3) |
| RT fraction delivered, Median (IQR) | 6 (5-15) |
| RT dose delivered, Median (IQR) | 4500 (3000 - 6000) |
| Dose Painting - Yes, n (%) | 55 (42.6) |
| Intended Dose Median (IQR) | 6000 (4000 - 6750) |
| Mean RT length ± SD (Days) | 11.6 (8.5) |
| PTV volume (cm3), Median (IQR) | 94.4 (39.2 - 174.4) |
| Mean D95 ± SD (% of intended dose) | 97.7 (11.0) |
| Reirradiation - Yes, n (%) | 8 (6.2) |
| Surgery before RT, n (%) | 91 (70.5) |
| Systemic before RT, n (%) | 126 (97.7) |
| HAIP before RT, n (%) | 81 (62.8) |
| Lines of Chemo, Median (IQR) | 3 (2 - 4) |
| RFA before RT, n (%) | 45 (34.9) |
| RFA to RT lesions - Yes, n (%) | 13 (10.1) |
| TARE before RT - Yes, n (%) | 10 (7.8) |
| Embolization before RT, n (%) | 12 (9.3) |
| Number of liver lesions at RT, n (%) |  |
| 1 | 57 (44.2) |
| 2 | 43 (33.3) |
| 3 | 12 (9.4) |
| ≥ 4 | 16 (12.4) |
| Undetermined | 1 (0.7) |
| CEA at diagnosis, Median (IQR) | 15.7 (3.38 - 176.9) |
| CEA at RT, Median (IQR) | 18.7 (4.8 - 127.2) |
| Other sites of Metastasis, n (%) |  |
| None | 52 (40.3) |
| Lung | 27 (21.0) |
| Non-regional LN | 10 (7.8) |
| Lung and non-regional LN | 25 (19.3) |
| Other | 15 (11.6) |
| Mean lesion 1 dimension 2 ± SD | 35.2 (22.3) |
| Mean lesion 1 dimension 1 ± SD | 26.0 (17.9) |
| Freedom from local progression (FFLP), n (%) |  |
| Progression | 55 (42.6) |
| No progression | 67 (52.0) |
| Undetermined | 7 (5.4) |
| Mean FFLP (months) ± SD | 10.5 (8.4) |
| Any hepatic progression, n (%) |  |
| Progression | 99 (76.8) |
| No progression | 25 (19.4) |
| Undetermined | 5 (3.8) |
| FFLP (months), Median (IQR) | 9.4 (3.9 - 15.0) |
| Months to any hepatic progression, Median (IQR) | 5.5 (2.0 -10.1) |

Abbreviations: LN = lymph node, RT = radiotherapy, PTV = planning target volume, CEA = carcinoembryonic antigen, HAIP = hepatic arterial infusion pump, TARE = transarterial radioembolization.

Supporting Table 1: A table of baseline clinical variables recorded as part of standard of care. The clinical variables will be utilized alongside computational radiomic features from computed tomography scans as input data to a machine learning model to predict local or any hepatic progression.

**Random Survival Forest Algorithm:**

To build a survival tree that predicts survival from an input vector of radiomic features, the following steps are taken:

1. Select *N* samples from the dataset.
2. For each sample *i = 1, 2, … N,* initialize a binary decision tree with max depth *D.*
3. At each node, iterate through set of features *X = {x­1­, x2, … xN}* and its range of feature values *S = {Smin, Smax}* to select feature *xi* and a threshold split value *si* such that:

Where *L(x,s)* is the log rank test such that

Where at time *ti*, *Ei*is the number of events at time *ti Ei,j* is the number of events at a daughter node *j, Yi* is the number of patients with an events or at risk at time *ti,* and *Yi,j*is the number of patients with an event or at risk at a daughter node *j*

1. Continue to grow children nodes unless the children node has no more than *M* surviving samples, where *M* is a user-defined hyperparameter
2. Calculate the cumulative hazard function for the decision tree with the Nelson-Aalen estimator:

Where *p* is a patient in the set of *M* patients in set *P = {p1,p2, … pM}*, *q* is a node in the set of *N* nodes in set *Q = {q1,q2, … qN}*, *Ep,q* is the number of events at time *tp,q*, and *Yp,q* is the number of patients with an event or at risk at time *tp,q*.

1. Repeat steps 1-5 *K* times to create *K* separately initialized trees, where *K* is a user-defined hyperparameter.
2. Average the cumulative hazard function over all trees to compute the ensembled cumulative hazard.

**List of Radiomic Features**

Supporting Table 1 shows a full list of radiomic features extracted from a liver volume.

|  |  |
| --- | --- |
| **Feature Category** | **Features** |
| First Order Statistics | Energy  Total Energy  Entropy  Minimum  10th Percentile  90th Percentile  Maximum  Mean  Median  Interquartile Range  Range  Mean Absolute Deviation  Robust Mean Absolute Deviation  Root Mean Squared  Standard Deviation  Skewness  Kurtosis  Variance  Uniformity |
| 3D Shape | Mesh Volume  Voxel Volume  Surface Area  Surface Area to Volume Ratio  Sphericity  Compactness  Spherical Disproportion  Maximum 3D Diameter  Maximum 2D Diameter (Axial)  Maximum 2D Diameter (Coronal)  Maximum 2D Diameter (Sagittal)  Major Axis Length  Minor Axis Length  Least Axis Length  Elongation  Flatness |
| Gray level Co-occurrence Matrix | Autocorrelation  Joint Average  Cluster Prominence  Cluster Shade  Cluster Tendency  Contrast  Correlation  Difference Average  Difference Entropy  Difference Variance  Difference Average  Joint Energy  Joint Entropy  Informational Correlation  Inverse Difference Moment  Inverse Difference Moment Normalized  Inverse Difference  Inverse Difference Normalized  Inverse Variance  Maximum Probability  Sum Average  Sum Entropy  Sum of Squares |
| Gray Level Size Zone Matrix | Small Area Emphasis  Large Area Emphasis  Gray Level Non-Uniformity  Gray Level Non-Uniformity Normalized  Size-Zone Non-Uniformity  Size-Zone Non-Uniformity Normalized  Zone Percentage  Gray Level Variance  Zone Variance  Zone Entropy  Low Gray Level Zone Emphasis  High Gray Level Zone Emphasis  Small Area Low Gray Level Emphasis  Small Area High Gray Level Emphasis  Large Area Low Gray Level Emphasis  Large Area High Gray Level Emphasis |
| Gray Level Run Length Matrix | Short Run Emphasis  Long Run Emphasis  Gray Level Non-Uniformity  Gray Level Non-Uniformity Normalized  Run Length Non-Uniformity  Run Length Non-Uniformity Normalized  Run Percentage  Gray Level Variance  Run Variance  Run Entropy  Low Gray Level Run Emphasis  High Gray Level Run Emphasis  Short Run Low Gray Level Emphasis  Short Run High Gray Level Emphasis  Long Run Low Gray Level Emphasis  Long Run High Gray Level Emphasis |
| Gray Level Dependence Matrix | Small Dependence Emphasis  Large Dependence Emphasis  Gray Level Non-Uniformity  Dependence Non-Uniformity  Dependence Non-Uniformity Normalized  Gray Level Variance  Dependence Variance  Dependence Entropy  Low Gray Level Emphasis  High Gray Level Emphasis  Small Dependence Low Gray Level Emphasis  Small Dependence High Gray Level Emphasis  Large Dependence Low Gray Level Emphasis  Large Dependence High Gray Level Emphasis |
| Neighboring Gray Tone Difference Matrix | Coarseness  Contrast  Busyness  Complexity  Strength |

Supporting Table 2: A list of radiomic features extracted from a liver volume. The features include computations related to the statistics, shape, and gray-level relationships of the image.

**Full Subset Analysis Accuracies**

|  |  |  |
| --- | --- | --- |
| **Input Features** | **Concordance Index (95% CI)** | **Integrated Brier Score (95% CI)** |
| **(No Feature Selection, Local Progression as Outcome)** | | |
| Other Clinical Data | 0.64 [0.54, 0.75] | 0.18 [0.15, 0.22] |
| Imaging Clinical Data | 0.66 [0.61, 0.71] | 0.17 [0.14, 0.20] |
| Treatment Clinical Data | 0.69 [0.62, 0.77] | 0.17 [0.14, 0.20] |
| All Clinical Data | 0.67 [0.58, 0.75] | 0.16 [0.15, 0.18] |
| Radiomics: Tumor Volume | 0.64 [0.52, 0.76] | 0.18 [0.17, 0.18] |
| Radiomics: Liver Parenchyma | 0.61 [0.53, 0.69] | 0.21 [0.19, 0.23] |
| Radiomics: Liver Parenchyma + Tumor | 0.66 [0.58, 0.74] | 0.2 [0.17, 0.22] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.66 [0.59, 0.73] | 0.19 [0.18, 0.21] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.64 [0.60, 0.68] | 0.19 [0.16, 0.22] |
| **(With Feature Selection, Local Progression as Outcome)** | | |
| Other Clinical Data | 0.66 [0.56, 0.76] | 0.19 [0.16, 0.22] |
| Imaging Clinical Data | 0.61 [0.56, 0.66] | 0.17 [0.14, 0.19] |
| Treatment Clinical Data | 0.72 [0.64, 0.79] | 0.18 [0.15, 0.21] |
| All Clinical Data | 0.62 [0.56, 0.69] | 0.19 [0.16, 0.22] |
| Radiomics: Tumor Volume | 0.68 [0.51, 0.84] | 0.19 [0.16, 0.24] |
| Radiomics: Liver Parenchyma | 0.66 [0.60, 0.72] | 0.20 [0.18, 0.22] |
| Radiomics: Liver Parenchyma + Tumor | 0.68 [0.62, 0.74] | 0.20 [0.16, 0.25] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.73 [0.64, 0.82] | 0.18 [0.15, 0.20] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.69 [0.65, 0.74] | 0.23 [0.21, 0.26] |
| **(No Feature Selection, Any Hepatic Progression as Outcome)** | | |
| Other Clinical Data | 0.57 [0.53, 0.61] | 0.16 [0.15, 0.16] |
| Imaging Clinical Data | 0.59 [0.55, 0.62] | 0.17 [0.15, 0.19] |
| Treatment Clinical Data | 0.56 [0.50, 0.61] | 0.14 [0.12, 0.16] |
| All Clinical Data | 0.59 [0.51, 0.67] | 0.14 [0.10, 0.17] |
| Radiomics: Tumor Volume | 0.58 [0.52, 0.65] | 0.17 [0.14, 0.20] |
| Radiomics: Liver Parenchyma | 0.56 [0.51, 0.61] | 0.14 [0.11, 0.18] |
| Radiomics: Liver Parenchyma + Tumor | 0.58 [0.53, 0.64] | 0.16 [0.12, 0.19] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.55 [0.51, 0.58] | 0.14 [0.12, 0.16] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.59 [0.51, 0.67] | 0.14 [0.10, 0.17] |
| **(With Feature Selection, Any Hepatic Progression as Outcome)** | | |
| Other Clinical Data | 0.60 [0.54, 0.67] | 0.16 [0.15, 0.17] |
| Imaging Clinical Data | 0.61 [0.56, 0.66] | 0.15 [0.14, 0.16] |
| Treatment Clinical Data | 0.63 [0.60, 0.66] | 0.13 [0.12, 0.15] |
| All Clinical Data | 0.59 [0.65, 0.74] | 0.15 [0.14, 0.16] |
| Radiomics: Tumor Volume | 0.61 [0.57, 0.66] | 0.19 [0.18, 0.21] |
| Radiomics: Liver Parenchyma | 0.59 [0.51, 0.66] | 0.16 [0.15, 0.18] |
| Radiomics: Liver Parenchyma + Tumor | 0.60 [0.54, 0.66] | 0.17 [0.14, 0.20] |
| Treatment Clinical Data + Radiomics from Liver Parenchyma and Tumor | 0.65 [0.61, 0.69] | 0.14 [0.12, 0.17] |
| All Clinical Data and Radiomics from Liver Parenchyma + Tumor | 0.69 [0.63, 0.74] | 0.14 [0.11, 0.17] |

Supporting Table 3: A summary of cross-validation accuracies for all tested subsets, including when using any hepatic progression as an outcome. Although any hepatic progression was not the primary endpoint of this study, the model was able to predict the outcome with slightly lower C-index results than utilizing local progression as the outcome.