**Title:**

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

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**Abstract:**

**Background:**

Prognostic assessment of colorectal liver metastases is essential for guiding patient management. Existing assessment criteria involve scoring from clinicopathological variables with limitations on 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.

**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 machine learning algorithm (RSF). 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 dosimetric input data, the model achieved a C-index of 0.73 (CI: 0.64 – 0.82). The most consistently predictive radiomic feature was gray tone difference matrix strength (feature importance: 3.32, CI: 2.50 – 4.15). The most predictive dosimetric feature was maximum dose (feature importance: 3.73, CI: 2.25 – 5.22).

**Conclusions**

The AI radiomics model achieves high local control prediction accuracy, 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:**

**Background:**

Patients with colorectal cancer develop colorectal liver metastases (CLM) in approximately 50% of cases [1], with a 12-month recurrence rate of approximately 40%. Surgery is the standard of care for patients that present with CLM in solitary or oligometastatic state, with reported 5- year survival ranging from 28-58% [2]. Studies with non-surgical liver-directed local therapy for CLM have yielded mixed results, external beam radiation therapy (EBRT) has emerged as an alternative, non-invasive approach for localized therapy of CLM in patients who are not otherwise eligible for surgical resection. 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 [3]. 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 computational information from radiomic features in computed tomography (CT) scans combined with machine learning methods to predict local control outcomes in CLM.

**Existing Work:**

Several methods have been published that predict clinical outcomes in CLM patients. A common method utilizes multivariate Cox proportional hazard regression using clinically relevant variables, selecting variables with the highest hazard ratio to create a scoring system [2, 5-12]. Brudvik et al. [12] utilized 6 clinicopathological characteristics, from which they selected three variables (node-positive tumor, metastases greater than 50mm, and RAS mutation) with with highest significance to create a 3-point scoring system. This scoring system achieved a concordance index (C-Index) of 0.66 (95% CI: 0.56-0.75) for predicting recurrence free survival on internal data validation.

There are several opportunities to improve on existing methods. First, the Cox model involves an exponential hazard function in the following form:

Where *h0(t)* is the baseline hazard function when covariates are zero, *βi* is the i-th parameter optimized by the partial likelihood function of variable *xi* and *h(t)* is the hazard function at time *t* [13]. The limitation is that variables in the model are parameterized in a linear combination, and the Cox model may not sufficiently characterize nonlinear dependencies between the variables.

Secondly, the existing studies use Cox regression to extract significant variables (p<0.05) and use a manual scoring system to map the variables to a prediction. A linear combination scores is susceptible to nonlinear confounding. Scoring systems that rely on integer scores for convenience are potentially unoptimized as thresholds for risk stratification may not be exactly at an integer value.

Thirdly, the studies were restricted in analyzing only clinicopathological variables. As tumor progression results in changes in liver tissue, there may be observable structural changes in the liver associated with survival. Rahmim et al. [14] utilized volumetric and heterogeneity measurements from positron emission tomography scans of 52 patients as input variables to a Cox hazard regression. Metabolic tumor volume (HR = 1.44-5.12) and total lesion glycolysis (HR = 1.38-4.98) were found to be significant and highly correlated with survival.

Wang et al. [15] evaluated nine different survival prediction scoring systems and found six to result in a concordance index (C-index) crossing the 0.50 threshold in its 95% confidence interval, with their own scoring system resulting in a C-index of 0.642 (95% CI: 0.570–0.713) using KRAS mutation and "poor chemotherapy response" as input to their Cox model.

Thus, an automated nonlinear survival model that uses of imaging features may address the limitations of existing models.

**Motivation and Contribution**

Our survival prediction model was built from two motivating ideas: the usage of radiomic imaging features as input data and modelling survival with machine learning.

CT has been standard of care for characterizing tumors by a trained expert. Radiomic features are computed attributes of a CT image which quantitatively characterize shape, intensity statistics, and gray-level relationships within the anatomy of interest. Differences in radiomic features have observed for different prognoses of liver metastases with Creasy et al. [16] and Simpson et al [17] observing that increased homogeneity was associated with increased risk of hepatic recurrence. Characterizing CT scans quantitatively with computer-aided methods such as radiomics provides the benefits of automated, consistent, and detailed observations of shape and texture, which can be used in the construction of predictive models.

To address the challenge of modelling variables which may not necessarily be linearly related, nonlinear and automated methods are required. Artificial intelligence (AI) methods have shown potential in survival prediction in previous studies [18, 19] A major strength of AI methods, specifically machine learning, are their automated iterative approach, where 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 model.

The main contributions of this work is the development of an automated survival prediction system, including automated extraction of radiomic features from CT liver scans, machine learning prediction model to utilize radiomic features to predict survival, and the evaluation of the performance of the model when compared to utilizing clinical data only.

**Materials and Methods**

**Patient Demographics:**

Patient demographics and baseline clinical variables are displayed in Table 1. Only variables obtained as standard of care for radiotherapy were selected.

|  |  |
| --- | --- |
| **Characteristics** | **All lesions (n=129)** |
| Number of patients/lesions | 97/129 |
| Sex, n (%) |  |
| Male | 83 (64.3) |
| Female | 46 (36.7) |
| Metastasis at time of diagnosis, n (%) |  |
| M0 | 40 (30.0) |
| M1 | 89 (70.0) |
| Colorectal Histology, 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 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) |
| Pump 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) |
| Y90 before RT - Yes, n (%) | 10 (7.8) |
| Embolization before RT, n (%) | 12 (9.3) |
| CEA at diagnosis, Median (IQR) | 15.7 (3.38 - 176.9) |
| CEA at RT, Median (IQR) | 18.7 (4.8 - 127.2) |
| 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) |
| Other sites at RT, 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) |

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.

**Data Collection and Equipment:**

Data for a total of 129 lesions from N=97 patients undergoing radiation treatment for CLM were retrospectively obtained from Memorial Sloan Kettering Cancer Center (MSKCC), including pre-treatment CT scans, dosimetric data, and outcome data. Right-censored time-to-event data was collected for two outcomes related to progression of disease, namely progression anywhere in the liver and local progression in the treated tumor. The study was approved by the MSKCC research ethics board (ID: 16-328). Liver and tumor volumes were segmented by radiation oncologists at MSKCC, as is standard of care. The AI model was programmed in Python, utilizing the Pyradiomics and Pysurvival libraries.

**Problem Definition**

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, has been 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, visualized in Figure 2.

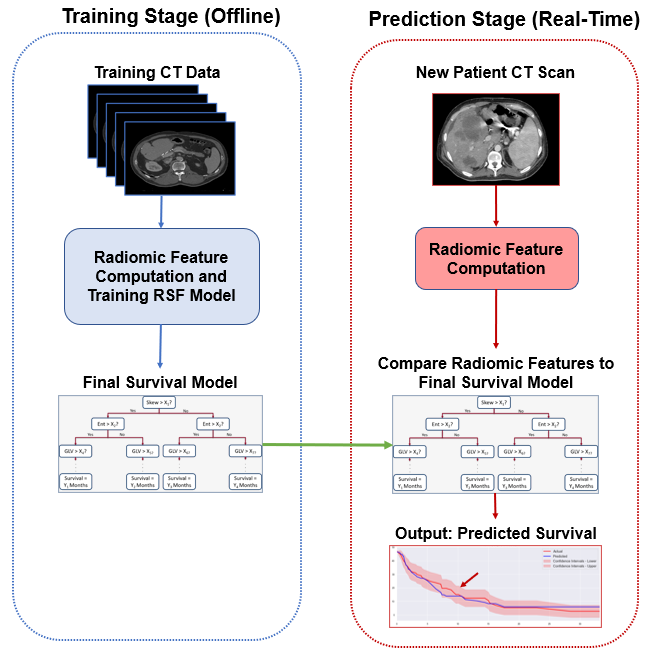


Figure 1: A visualization of the survival prediction system. The system contains two stages. The first is a training stage, where a survival model is built by training a random survival forest from radiomic features extracted from a set of computed tomography liver scans. Once the survival model has 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.

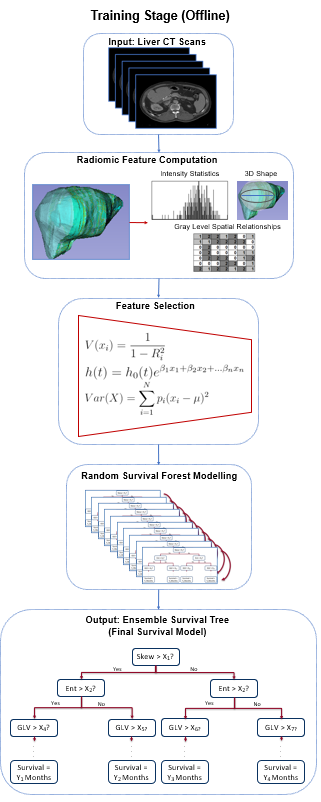


Figure 2: Steps involved in training the prediction model. The computed tomography scans of the training set are first processed by extracting the liver volumes and computing radiomic features on the volumes. Feature selection is used to filter variables with low information yield and the remaining features are used to build a decision tree using the random survival forest algorithm. The final output is an optimized ensemble survival tree which predicts survival given a set of radiomic features.

**Radiomic Feature Extraction**

In the first stage to train the model, 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 Supplemental Table 1. A visualization of radiomic feature extraction is displayed in Figure 3.

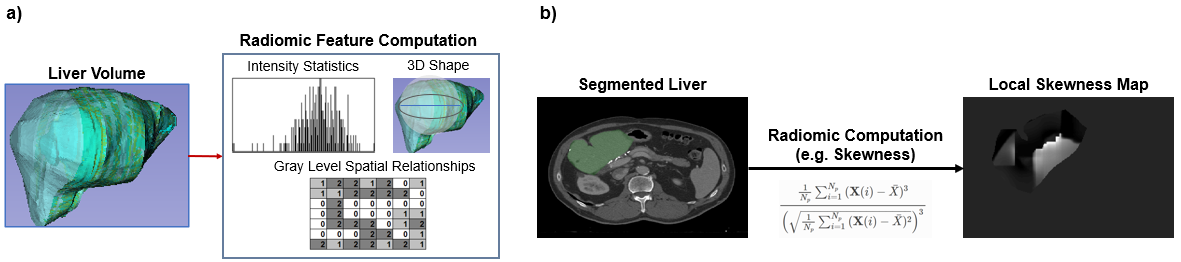


Figure 3: Visualization of radiomic feature extraction. a) A liver volume is extracted from the computed tomography scan and features relating to the intensity statistics, shape, and gray level matrices of the live volume are computed. b) An example of one such radiomic feature, skewness, from a liver 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 to inclusion of irrelevant or redundant features. Hence, several feature selection strategies have been employed. First, variance thresholding was performed to remove any feature with no variance. Next, redundant features were removed using a variance inflation factor threshold of 10 as an indicator of collinearity [20].

If the number of samples are not sufficient for the dimensionality of the feature space, then overfitting is likely to occur [21]. To further reduce the feature set we therefore scored the relevance of the remaining features using the hazard ratios predicted for each variable in a Cox proportional hazards model [22], and removed less relevant features until the ratio of features to samples was less than 1:10. This additional step is dependent on the sample size and with sufficient samples in future studies may be unnecessary.

**Random Survival Forest Model**

To predict survival from the filtered feature set, the random survival forest (RSF) algorithm was used [23]. The RSF algorithm operates by creating an ensemble decision tree with nodes representing features with a threshold value. The features used for the nodes and the threshold values were adjusted with each pass of patient data to maximize the log-rank test given by:

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. The cumulative hazard was calculated by the Nelson-Aalen estimator [24]. A detailed outline of the algorithm is available in the Supplemental Information section. Hyperparameters, including maximum number of trees, maximum number of patients for a terminal node, and maximum depth, were optimized with a gridsearch algorithm that occurs within a cross-validation loop. After optimization, feature importances were computed by the difference between the error rate and the perturbed error rate for that feature.

**Validation**

A 4 k-fold cross-validation scheme was used to provide multiple estimates of the performance of the model. In this type of scheme, the dataset is shuffled and partitioned into 4 equal sized subsets. Each subset 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 using the same overall approach. The concordance index (C-index) and integrated Brier score (IBS) were used as accuracy metrics to evaluate the models in each fold. The final reported accuracy was computed by averaging the C-index and IBS over the 4 k-folds.

Ablation analysis was performed to investigate the performance of the model when adjustments to individual components were made. First, we defined 6 different feature sets:

1. Non-imaging and non-dosimetric clinical data: baseline patient variables not related to dosimetric information or tumor geometry from CT imaging
2. Dosimetric clinical data: variables related to dosage
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. All cinical data and Radiomics from liver parenchyma + tumor: The union of feature sets 4. And 7.

Table 2 displays a list of categorized clinical variables.

|  |  |
| --- | --- |
| **Category** | **Variables** |
| Imaging clinical variables | Number of lesions at radiotherapy  Other sites at radiotherapy  Lesion dimension 1  Lesion dimension 2  Planning target volume (cm3) |
| Dosimetric clinical variables | Biologically effective dose (Gy)  Minimum dose for planning target volume (cGy)  Maximum dose (cGy)  Dose for 95% of target volulme (% of intended prescribed dose)  Systemic treatment before radiotherapy  Lines of chemotherapy  Pump before radiotherapy  Carcinoembryonic antigen at radiotherapy  KRAS mutation |
| Non-imaging and non-dosimetric clinical variables | Histology  Metastasis at diagnosis  Number of liver lesions at diagnosis  Other sites at diagnosis  Liver location  Reirradiation  Surgery before radiotherapy  Ablation before radiotherapy  Y90 before radiotherapy  Embolization before radiotherapy  P53 mutation  BRAF mutation  Microsatellite stability |

Table 2: The categorization of clinical variables to imaging, dosimetric, and non-imaging and non-dosimetric 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 twice, once with the outcome being local progression and once with the outcome being any hepatic progression, resulting in 18 models. This was repeated with and without the feature selection stage, resulting in a total of 36 models to be evaluated. 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 averaged cross-validation accuracies are summarized in Table 3. Samples of the predicted survival and IBS curves compared to the ground truth are visualized in Figure 4. 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)** | | |
| Non-Imaging and Non-Dosimetric 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] |
| Dosimetric 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] |
| Dosimetric 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)** | | |
| Non-Imaging and Non-Dosimetric 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] |
| Dosimetric 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] |
| Dosimetric 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)** | | |
| Non-Imaging and Non-Dosimetric 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] |
| Dosimetric 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] |
| Dosimetric 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)** | | |
| Non-Imaging and Non-Dosimetric 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] |
| Dosimetric 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] |
| Dosimetric 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] |

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.

We note that nearly all input dataset variations resulted in a C-index greater than 0.50 within 95% confidence interval ranges. The greatest accuracy occurred when combining both radiomics of the liver parenchyma and tumor volume with dosimetric data to predict local progression (C-index: 0.73 [0.64, 0.82]). Utilizing only radiomic data from the liver parenchyma and tumor volume to predict local progression resulted in a C-index of 0.68 [0.62, 0.74]. The IBS of all models were below 0.25, which is the standard threshold to indicate nonrandom prediction [25].

Graphical user interface

Description automatically generated

Figure 4: Comparison of the predicted survival (red) from the random survival forest compared to the actual survival (red) from a Kaplan-Meier model of the outcome data. Comparison include the best k-fold (left) and worst k-fold (right) during cross-validation from using either radiomics and dosimetric data (top), radiomics data only (middle), or dosimetric data only (bottom). All models achieved a higher C-index than models from previous studies and the usage of radiomic features enhances the accuracy of the model.

|  |  |
| --- | --- |
| **Feature (Dosimetric Only)** | **Importance Score (95% CI)** |
| Max 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] |

Table 3: The feature importances for the random survival forest model utilizing dosimetric features as input data with no radiomic features. Max dose was observed to be the most predictive feature, significantly with more information gain than any other dosimetric feature.

|  |  |
| --- | --- |
| **Feature (Radiomics on Liver Plus Tumor Volume Only)** | **Importance Score (95% CI)** |
| 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] |

Table 4: The feature importances for the random survival forest model utilizing radiomic features extracted from the liver and tumor volume as input data with no dosimetric features. Gray tone difference matrix computations yielded the most predictive features and it is observed that the differences in predictivity is less than with dosimetric features, where Max Dose was overwhelmingly the most predictive variable.

|  |  |
| --- | --- |
| **Feature** | **Importance Score (95% CI)** |
| Max 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 5: The feature importances for the random survival forest model when utilizing both dosimetric and radiomic features. As expected, both gray tone difference matrices and max dose features resulted in high predictive value. However, the importance of max dose was decreased compared to when using only dosimetric 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 strength, though with a large variance in importance over the 4 k-folds. The features that were assessed were all filtered features, hence, the majority of the radiomic features extracted were not used in modelling nor were their importances computed. The most predictive clinical variable was the dosimetric feature of maximum dosage, having the greatest feature importance beyond the 95% confidence interval of any other clinical feature. However, in the combined radiomics and dosimetric data model, the feature importance of maximum dose decreased, indicating that other radiomic features can predict survival even with maximum dose ignored.

**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. In this study, radiomic features from a liver CT scan and clinical variables were used as input to a random survival forest was evaluated by comparing predicted survival to actual outcome data to evaluate prediction performance especially compared to previous methods. 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 [25]. An additional strength of our study is that our method was cross-validated 4 times, rather than testing on the same data used for modelling in order to prevent inflated accuracies due to overfitting.

Without feature selection, although the survival model performed with an average C-index greater than 0.55, there was a large variance in performance across the cross-validation folds and the accuracy overall was less than that with feature selection. 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. With higher dimensionality, the model is susceptible to overfitting to the training data, especially if there are insufficient number of samples to train the model, resulting in a lower accuracy in the testing data.

As discussed in the Existing Work section, most prior studies reported a C-index lower than 0.60 when tested on dataset that was not used in creating the prediction model, with one study achieving a C-index of 0.64 [12]. Utilizing clinical data that excludes dosimetric variables resulted in prediction C-indices within this range, though we did not have access to three of the variables in the model by Wang et al. [15]. In future studies, a fairer comparison between manual scoring systems and automated RSF methods could be done by ensuring that all clinical variables used to produce the score are available to the RSF. Utilizing radiomic models of the liver parenchyma and tumor model or dosimetric data exceeded the best performing model from previous studies.

The best performing radiomic model was utilizing radiomic features extracted 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 C-index accuracy is greater than any previous studies to our knowledge. An RSF model trained from dosimetric data resulted also in a high accuracy with a C-index (95% CI) of 0.72 (0.64 – 0.79). When combining both, the high accuracy is retained, which a C-index (95% CI) of 0.73 (0.64, 0.82). In the combined mode, the two most predictive features were max dose with a feature importance score (95% CI) of 3.83 (1.05 – 6.62) and neighboring gray tone difference matrix strength with a feature importance score (95% CI) of 1.90 (0.93 – 2.86). Moreover, the feature importance (95% CI) of max dose decreased from 10.84 (6.35, 15.34) in the dosimetric data only model, indicating that the radiomic features contribute to prediction even when combined with dosimetric data. 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 leading to a different prognosis. This is consistent with findings from Simpson et al. [17], who observed that increased homogeneity of liver texture is associated with recurrence.

The accuracy of the RSF has two major implications. First, radiomic features provide predictive information related to 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 the volume, 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 are either protective or susceptible to recurrence. For instance, kurtosis measures the weight of the tails in a distribution and with kurtosis being 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 our 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. The model was able to achieve a C-index greater than previous studies, however, further validation with a diverse patient population from different centers for instance can evaluate the generalizability of the model with greater statistical power. A wide uncertainty in C-index values indicates that when tested on a different subset of patients, the model accuracy is not consistent. In our study, we limited the cross-validation to 4 k-folds. With a larger sample size, higher-order cross-validation, such as with 5 k-folds or 10 k-folds, may be conducted to have more testing sets so that evaluation of the model has more statistical power. Feature selection may not be necessary with sufficient samples as with sufficient computational power, a random forest can in theory filter variables that have low predictive information gain [26]. Future studies may also include patients before and after radiotherapy, as texture in CT scans may change after treatment.

Although the model accuracy supports the idea that the radiomic features are predictive, we are limited in the medical interpretation of these 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, although our study can assess the performance of a survival model, the features determined to be predictive require future studies to understand how they can be descriptive of the pathophysiology of metastases.

**Conclusion**

We have developed a time-dependent survival prediction model 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 dosimetric 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.

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**Supplemental Information:**

**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 1: 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.