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Original Research Article

Radiomics-based Machine Learning Approach to Predict Chemotherapy Responses in Colorectal Liver Metastases

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Abstract

Objectives: This study explored the clinical utility of CT radiomics-driven machine learning as a predictive marker for chemotherapy response in colorectal liver metastasis (CRLM) patients.

Methods: We included 150 CRLM patients who underwent first-line doublet chemotherapy, dividing them into a training cohort (n=112) and a test cohort (n=38). We manually delineated three-dimensional tumor volumes, selecting the largest liver metastasis for measurement, using pretreatment portal-phase CT images and extracted 107 radiomics features. Treatment response was classified as responder (complete or partial response) or non-responder (stable or progressive disease), based on the best overall response according to RECIST criteria, version 1.1. Employing Random Forest and Boruta algorithms, we identified significant features for responder-non-responder differentiation. Radiomics signatures were developed and validated in the training cohort using five-fold cross-validation, and performance was assessed using the area under the curve (AUC).

Results: Among the patients, 91 (61%) were responders and 59 (39%) were non-responders. Variable selection with Boruta revealed three key parameters ("DependenceVariance," "ClusterShade," and "RunVariance"). In the training cohort, individual CT texture parameter AUCs ranged from 0.4 to 0.65, while the machine learning analysis incorporating all valid parameters exhibited a significantly higher AUC of 0.94 ($p < 0.01$). The validation cohort also demonstrated strong predictive accuracy, with an AUC of 0.87 for treatment response.

Conclusions: This study highlights the potential of CT radiomics-driven machine learning in predicting chemotherapy responses among CRLM patients.

Keywords

machine learning, CT texture analysis, colorectal cancer, liver metastases, chemotherapy

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related deaths[1]. Furthermore, liver metastasis is the most common type, occurring in 30%-50% of colorectal cancer patients[2-4]. Patients with colorectal liver metastases (CRLM) generally present with unresectable disease. The treatment of metastatic colorectal cancer (mCRC) has advanced significantly in the last 20 years. These improvements have mainly been driven by the availability of novel targeted agents and biomarkers[5-8]. In particular, molecular biomarkers have been identified for patients who are candidates for agents targeting EGFR and HER2, TRK fusion, and immunotherapy[9-11]. Despite these advances in molecular biomarkers, the clinical outcomes of unresectable CRC remain inadequate, and further development of novel biomarkers is required.

Computed tomography (CT) texture analysis is an imaging technique involving quantifying spatial heterogeneity and extracting pixel spatial intensity variations across tissues of interest[12]. Accumulating evidence indicates that CT texture analysis of CRLM provides a promising strategy to predict responses to chemotherapy[13-15]. However, the datasets generated by these analyses, particularly those derived from three-dimensional CT (3D-CT) texture analysis, are formidable in size and complexity.

Recent developments in radiomics-based machine learning have offered a compelling solution to enhance prediction accuracy by distilling actionable rules and algorithms from intricate data[16-18]. Several studies have assessed the potential of CT radiomics-based machine learning to improve chemotherapeutic response predictions and confirm the hypothesis that greater tumor heterogeneity indicates chemotherapy sensitivity[19-21]. However, the value of CT radiomics-based machine learning in predicting the chemotherapeutic responses of liver metastases has not yet been demonstrated.

In light of these considerations, our study aimed to examine the clinical efficacy of CT radiomics-based machine learning as a predictive tool for systemic chemotherapy responses in patients grappling with the formidable challenge of CRLM. Through a comprehensive examination of radiomics features and machine learning algorithms, we aim to provide valuable insights into the predictive potential of this innovative approach, holding promise for enhancing treatment outcomes in this patient population.

Methods

Patients

From January 2005 to January 2019, we performed a retrospective analysis of 150 consecutive patients with liver metastasis who received first-line chemotherapy for mCRC at Kumamoto University Hospital (Kumamoto, Japan). The eligibility criteria included histologically confirmed CRC, measurable metastatic disease according to Response Evaluation Criteria in Solid Tumors (RECIST), no previous treatment for metastatic disease, and treatment with oxaliplatin of irinotecan-based doublet chemotherapy. The exclusion criteria included patients without a whole-body enhanced CT scan one month before first-line chemotherapy. CT was performed at 3-month intervals until disease progression or death. Additionally, EOB-MRI and PET-CT were not conducted in all patients, and these modalities were reserved for cases with specific clinical indications that justified their use. The response to treatment was evaluated according to the RECIST criteria, version 1.1, with the best overall response during the treatment period being recorded. Patients who showed partial (PR) or complete response (CR) were considered responders, whereas patients who showed progression (PD) or stable disease (SD) were classified as non-responders.

All patients provided informed consent, including consent for their clinical data and images to explore radiomics parameters. All patients could revoke their consent before revocation becomes impracticable, as in the case of samples being unlinkable anonymized. This retrospective study was approved by the institutional review board of our hospital (no. 2000) and conducted in accordance with the Declaration of Helsinki. This study adhered to the REporting recommendations for tumor MARKer prognostic studies (REMARK)[22].

CT scanning and contrast injection protocols

All patients were scanned with multi-detector row CT scanners (40 to 320 rows). All CT studies were performed during a single-breath-hold with the patient in the supine position. The CT scanning parameters were 0.5-sec rotation scan, 5.0-mm detector row width, 120 kVp, and automatic tube current modulation. The scanning time varied from 3 to 10 sec depending on the geometry and CT scanners. The contrast material dose was tailored using the patient's body weight (600 mgI/kg) and injected in 30 seconds. Portal venous phase (PVP) CT scanning was performed 70 sec after the start of the contrast material injection. The PVP images of the liver were reconstructed with a 5-mm slice thickness.

Computation of radiomics features

We imported Digital Imaging and Communications in Medicine images to compute texture features into 3D Slicer software (version 4, http://www.slicer.org). One investigator (23 years of experience in abdominal CT) then manually traced the outer edge of each metastatic liver tumor on 3D CT images and selected a volume of interest (VOI) for the

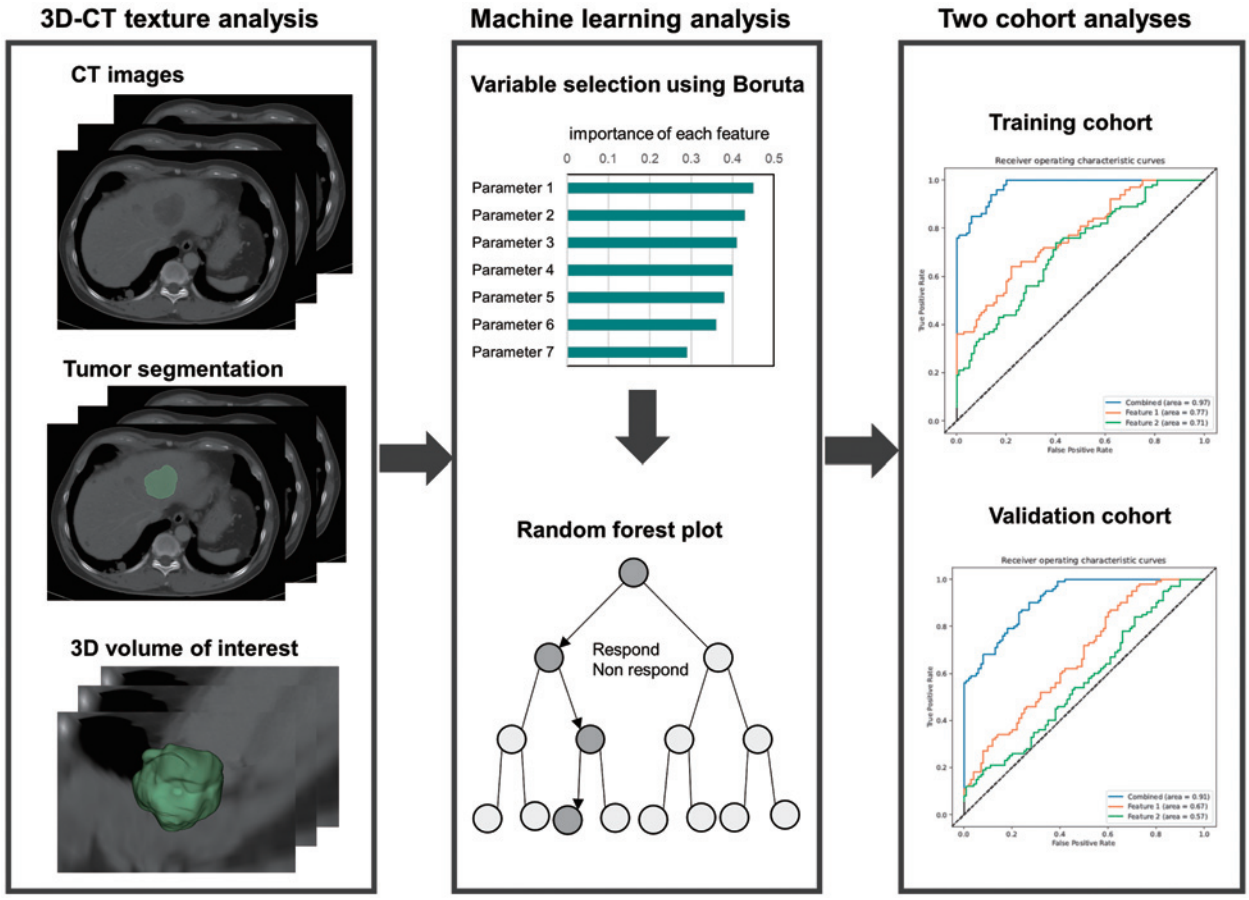

Figure 1. The workflow of CT radiomics-based machine learning analysis.
The tumor lesions were manually segmented from pretreatment contrast-enhanced CT images, and the three-dimensional tumor volume of interest was constructed. The radiomics parameters were then extracted. Significant features for differentiating between responders and nonresponders were selected using the Random Forest and Boruta algorithms. Finally, the performance of the machine learning models was evaluated using the independent test cohort.

radiomics analysis. In cases with multiple liver metastases, the largest and most reliably traceable tumor was selected. In addition, necrotic, cystic areas, or calcifications were included for analysis. A total of 107 radiomics features (14 shape features, 18 first-order intensity statistics features, and 75 texture features) were extracted using the 3D Slicer software extension, SlicerRadiomics (V2.10, http://download.slicer.org)[23]. Tumor segmentation was repeated for 20 randomly selected cases to assess reproducibility, with Lin's concordance correlation coefficient for the mean value of CT texture features being 0.91.

Machine learning analysis (Figure 1)

We used free programming software (Python, version 3.8; https://www.python.org/) and the scikit-learn machine learning library (version 0.18.1, http://scikit-learn.org/stable/) for radiomics analysis. We randomly divided 150 patients into groups of 112 and 38 for training and test data, respectively, with the "train test split" function in the scikit-learn machine learning library. Most machine learning models classify objects by the distance between two points, and when the variation in a specific feature is extremely large, the distance is governed by this particular feature. Therefore, we performed simple normalization using the "StandardScaler().fit_transform" function in the scikit-learn library.

Various feature selection algorithms and machine learning models, including LASSO, Support Vector Machines, and Gradient Boosting, were initially considered; however, the Boruta and Random Forest algorithms were ultimately chosen because of their robustness in handling high-dimensional data and their abilities to provide interpretable results[24], which are essential for identifying significant radiomic features.

Significant features for differentiating responsive and nonresponsive metastatic liver tumors were selected using the Boruta algorithms[25] in the training group. Boruta creates dummy features that should not contribute to discrimination and uses real and dummy features to train a Random Forest (RF) classifier, one of the major ensemble machine learning algorithms[26]. Next, it compares the importance of the real

and fake features, and features are selected only if their importance values are significantly greater than the maximum importance values of dummy features. These selected features were sorted in descending order of importance. A higher position of a feature among selected features indicated greater significance and better predictive value of the feature for the model created. Finally, the Random Forest was trained and validated with all significant features to differentiate between responsive and non-responsive metastatic liver tumors using 5-fold cross-validation in the training data. The performance of all models was also evaluated using the test data.

Statistical analysis

Statistical analyses were performed with Python software (ver. 3.9, Python Software Foundation, Wilmington, Del) and JMP software (ver. 10, SAS Institute Inc, USA). All data are expressed as median (interquartile range). Mann-Whitney U and χ^2 tests were used to compare groups and proportions between groups, respectively. We calculated feature importances using SHAP (Sharpley Additive exPlanations). The area under the curve (AUC) of receiver operating characteristic (ROC) curves obtained by the machine learning classifier was calculated for both datasets. In addition, the AUC of selected features was calculated to differentiate between responsive and non-responsive metastatic liver tumors. Finally, the AUC of the machine learning classifier was compared with all selected features using the Delong test. Differences of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics

In total, 150 patients were enrolled, as shown in Table 1, Figure 2. The median age was 64 years (range 33 to 86), and most patients were male (59%). Eastern Cooperative Oncology Group performance status scores were 0, 1, and 2 in 62%, 31%, and 7% of patients, respectively. Primary tumors were located in the right-sided colon (29%), left-sided colon (37%), and rectum (33%). The median follow-up time was 27.7 months. All 150 patients had at least one measurable liver lesion. The majority of patients (90%) received oxaliplatin-based doublet chemotherapy. Regarding targeted agents, 55% of patients received bevacizumab, and 21% received anti-EGFR antibodies. There was no significant difference in variables between the training and validation cohorts. Responses to treatment are also shown in Table 2. One patient achieved CR, and 90 (60%) showed PR. Thus, the overall best response rate was 61%. There was no significant difference in response to chemotherapy between the two cohorts.

Machine learning-based CT texture analysis

Three radiomics factors ("DependenceVariance," "ClusterShade," and "RunVariance") were extracted by variable selection using Boruta. The importance of these features is shown in Figure 3. In the training group, the AUC of the RF model using all three parameters was 0.94, which was significantly higher ($p < 0.01$) than the AUC of the "DependenceVariance" (AUC = 0.54), "ClusterShade" (AUC = 0.65), and "RunVariance" (AUC = 0.56) (Figure 4a). In the test group, the AUC of the RF model using all three parameters was 0.87, which was significantly higher ($p < 0.01$) than the AUC of the "DependenceVariance" (AUC = 0.56), "ClusterShade" (AUC = 0.62), and "RunVariance" (AUC = 0.64) (Figure 5a). Although there was substantial overlap in each feature between the two groups, they were separated to some degree by integrating the three features. The distribution of each feature in the response and non-response groups is shown in Figure 4b, 5b.

Representative cases

Representative cases are shown in Figure 6. The two representative cases were selected to illustrate the variable treatment outcomes, with one case showing a positive response to chemotherapy and the other exhibiting disease progression. These cases highlight the model's ability to distinguish between responders and non-responders based on pretreatment radiomic features.

Case 1 was a 56-year-old male patient with multiple liver metastases from sigmoid colon cancer. The machine learning-based CT texture analysis of pretreatment CT images classified this patient into the responder group, with a prediction accuracy of 0.973. The patient received FOLFOX plus bevacizumab. Post-treatment CT imaging (3 months later) demonstrated PR with decreased lesion size from 86.4 to 50.9 mm. The patient underwent a two-stage hepatectomy and was alive at the last follow-up 55 months after chemotherapy.

Case 2 was a 65-year-old male patient with multiple liver metastases from cecal colon cancer (*KRAS*-wild type tumor). After primary tumor resection, the patient was administered FOLFOX plus cetuximab. The machine learning-based CT texture analysis of pretreatment CT images classified this patient into the responder group, with a prediction accuracy of 0.973. Post-treatment CT imaging (2 months later) demonstrated progressive disease with an increase in lesion size from 18.9 to 27.3 mm. The patient did not respond to alternative systemic chemotherapy and died approximately 11 months after chemotherapy.

Discussion

We conducted this study to evaluate the value of CT

Table 1. Patient Characteristics.

Variables	All		Training cohort		Validation cohort		*P* value[a]
	N	(%)	N	(%)	N	(%)	
All	150		112	(75)	38	(25)	
Age, years (range)	64	(33-86)	63	(33-84)	66	(42-86)	0.41
Sex							0.86
Male	89	(59)	66	(59)	23	(61)	
Female	61	(41)	46	(41)	15	(39)	
EOCG-PS							0.84
Grade 0	93	(62)	68	(61)	25	(66)	
Grade 1	47	(31)	36	(32)	11	(29)	
Grade 2	10	(7)	8	(7)	2	(5)	
Timing of metastases							0.58
Synchronous	126	(84)	93	(83)	33	(87)	
Metachronous	24	(16)	19	(17)	5	(13)	
Primary tumor location							0.31
Right-sided colon	44	(29)	32	(29)	12	(32)	
Left-sided colon	56	(37)	39	(35)	17	(45)	
Rectum	50	(33)	41	(37)	9	(24)	
Extrahepatic disease							0.57
Yes	73	(49)	53	(47)	20	(53)	
No	77	(51)	59	(53)	18	(47)	
Primary tumor resection							0.30
Performed	58	(39)	46	(41)	12	(32)	
Not performed	92	(61)	66	(59)	26	(68)	
Number of liver metastases							0.52
1-4	66	(44)	51	(46)	15	(39)	
≥5	84	(56)	61	(54)	23	(61)	
Maximum size of liver metastases							0.93
≤5 cm	78	(52)	58	(52)	20	(53)	
>5 cm	72	(48)	54	(48)	18	(47)	
KRAS mutation status							0.33
Wildtype	83	(55)	63	(56)	20	(53)	
Mutation	39	(26)	26	(23)	13	(34)	
Unknown[b]	28	(19)	23	(21)	5	(13)	
Cytotoxic chemotherapy							0.45
Oxaliplatin-base	135	(90)	102	(91)	33	(87)	
Irinotecan-base	15	(10)	10	(9)	55	(13)	
Biotarget agents							0.99
Bevacizumab	83	(55)	62	(55)	21	(55)	
anti-EGFR antibody	31	(21)	23	(21)	8	(21)	
None	36	(24)	27	(24)	9	(24)	

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status, EGFR: Epidermal Growth Factor Receptor

a Based on the χ^2 test or the Kruskal–Wallis test when appropriate.

b Not included in the test.

radiomics-based machine learning of liver metastases in predicting chemotherapeutic responses in patients with CRLM. The Boruta algorithm ranked 107 (14 shape features, 18 first-order intensity statistics features, and 75 texture features) features. The results of this study demonstrated that CT texture analysis using artificial intelligence is useful for predicting chemotherapy responses. Machine learning is changing the field of medical imaging. By applying machine learning technology, we captured minute differences in CT images of liver metastases and successfully distinguished between chemotherapy-sensitive and insensitive liver metastases.

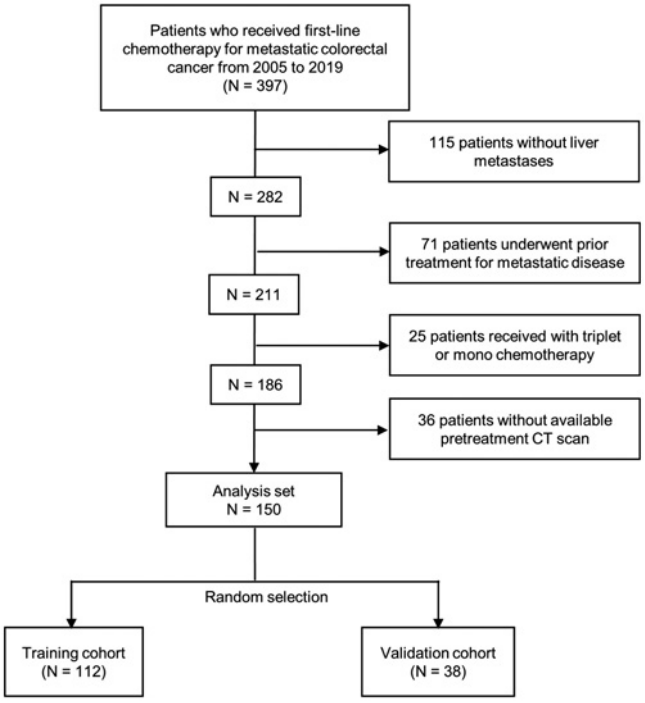

Figure 2. The patient flow of this study.

The present study obtained unique results among studies combining CT radiomics and machine learning. In contrast to several prior studies[27-29] that depended on pre- and post-treatment imaging to predict chemotherapy efficacy, our approach necessitates only pretreatment images. This distinction is crucial; while the former methodology provides retrospective insights, potentially delaying the implementation of optimal treatment plans, our predictive model enables early therapy customization. This is a significant advantage, as it allows for the adjustment of treatment strategies before the commencement of therapy, potentially improving patient outcomes. Moreover, while Qi et al.[30] focused on individual tumors, potentially limiting their model's broader clinical utility and achieving a lower predictive accuracy (AUC = 0.545), our study addresses these limitations by considering the patient as a whole, significantly enhancing the predictive precision (AUC = 0.87). Although Wei et al.[31] achieved high predictive accuracy using deep learning (AUC = 0.82), the "black box" nature of such models raises concerns about clinical interpretability and trust.

Recent studies have provided molecular biomarkers, including gene mutations[32], gene or miRNA expression levels[33-35], and ctDNA levels[36], to predict responses to systemic chemotherapy for mCRC. The predictive accuracy of these molecular biological markers was lower (AUC = 0.79) than that observed in this study (AUC = 0.87). Radiomics is based on discovering imaging features not identifiable by simple visual analysis or measurements[36], and three main processes are involved (VOI segmentation, texture analysis, and model development). Furthermore, contrast-enhanced CT remains the primary modality for staging patients with CRC, and no other special examination is required. Therefore, this method is less burdensome for patients and more accessible to apply clinically than other approaches.

In this study, three texture features ("DependenceVariance," "ClusterShade", and "RunVariance") were identified as predictable textures. These three features are termed texture-based metrics or second-order statistic features, and they analyze the spatial relationships between voxels with similar intensity values[37,38]. This provides information regarding the heterogeneity within the lesion[39]. Although we cannot explain why these three features were particularly effective for differentiation, previous studies have reported that texture features related to tumor heterogeneity are strongly associated with the expression of specific genes, and it is possible that a similar relationship exists in this study[40,41]. Additionally, as shown in the scatter plots, there were no simple relationships between these texture features, and a non-linear machine learning method, such as the RF used in this study, appeared to be necessary for prediction.

The results of this study demonstrated that CT radiomics-based machine learning is useful in predicting responses to chemotherapy. Future research will be conducted in the following areas. (1) In the palliative setting, the objective response rate is not the best indicator of treatment benefits. The same validation will be performed for survival prediction. (2) We aim to perform the same analysis for each patient treated with two types of molecular targeted drugs used in chemotherapy for CRC, including the angiogenesis inhibitor bevacizumab and an anti-EGFR antibody, to predict which molecular target drug is more useful. (3) One of the challenges in this study was the time-consuming extraction of liver metastases from pretreatment CT scans using 3D Slicer software. Automating this process will enable more objective extraction.

Certain limitations of our study should be acknowledged. First, the limited sample size and the disparity in the number of patients between responder and non-responder groups may reduce the statistical power of our results. Although this reflects real-world patient outcomes, future studies should aim for more balanced cohort sizes to enhance the robustness of the findings. Second, the study's retrospective design and inclusion of various doublet chemotherapy regimens prevent the results from providing specific predictions by treatment regimen. Furthermore, variations in CT equipment and chemotherapy protocols over the study period (2005-2019) may introduce additional variability. However, these variations also allow for the generalization of the results to patients with diverse backgrounds.

Table 2. Best Overall Response.

Objective response	All		Training cohort		Validation cohort		P value[a]
	N	(%)	N	(%)	N	(%)	
Complete response	1	(1)	1	(1)	0	(0)	0.73
Partial response	90	(60)	68	(61)	22	(22)	
Stable disease	43	(29)	30	(27)	13	(13)	
Progressive disease	16	(11)	13	(12)	3	(3)	
Responder	91	(61)	69	(62)	22	(58)	0.69
Nonresponder	59	(39)	43	(38)	16	(42)	

a Based on the χ^2 test or the Kruskal–Wallis test when appropriate.

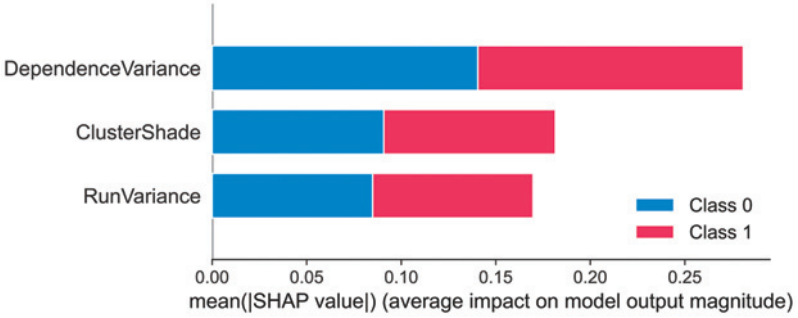

Figure 3. Importance of three radiomics features.
Three radiomics factors ("DependenceVariance," "ClusterShade," and "RunVariance") were extracted by variable selection using SHAP (Sharpley Additive exPlanations).

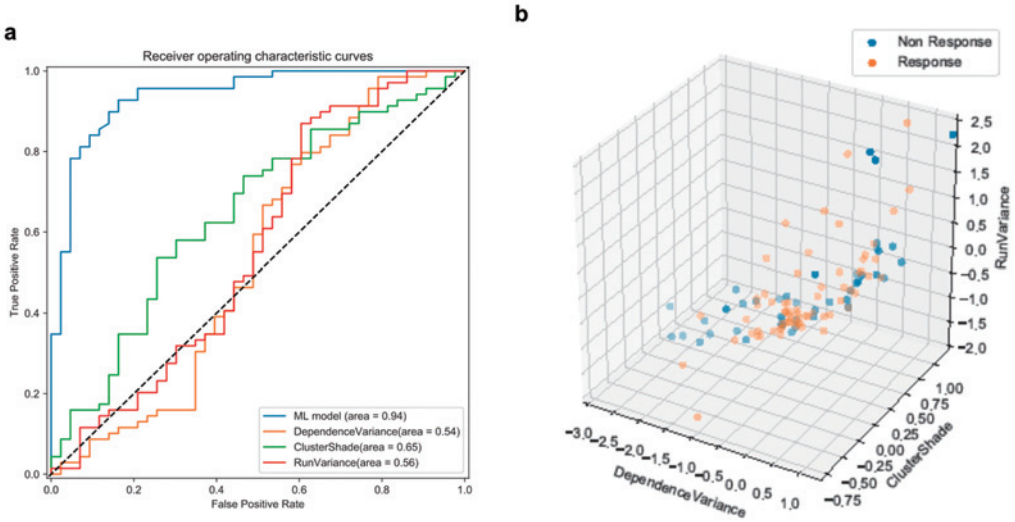

Figure 4. Machine learning-based CT texture analysis of liver metastases in the training cohort.
a) The AUC of the Support Vector Machine model using all parameters was 0.90.
b) Distribution of each feature in the response and non-response groups.

An additional limitation of this study was the manual segmentation of the VOI, which introduced subjectivity and potential bias, despite the investigator's extensive experience. The time required also limits the scalability of the protocol

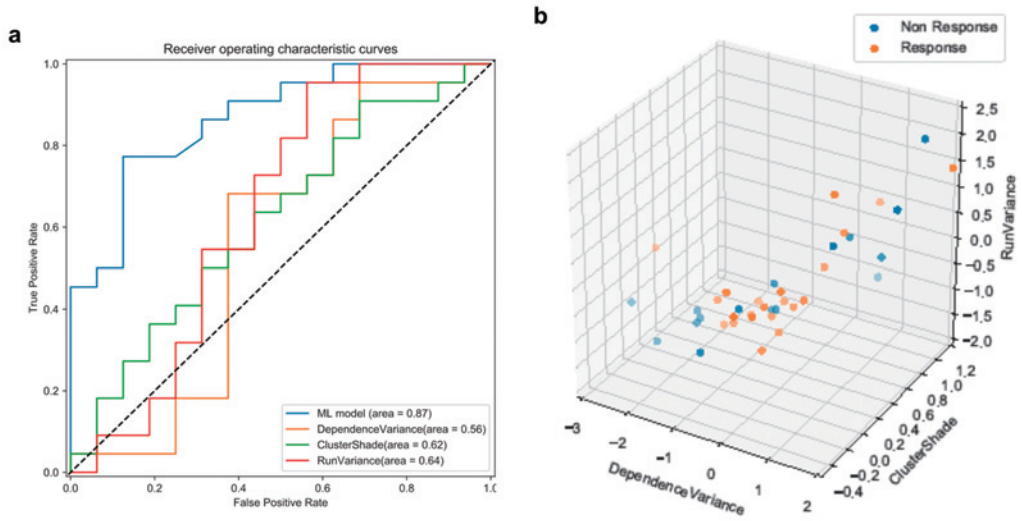

Figure 5. Machine learning-based CT texture analysis for liver metastases in the validation cohort.
a) The AUC of the Support Vector Machine model using all parameters was 0.87.
b) Distribution of each feature in the response and non-response groups.

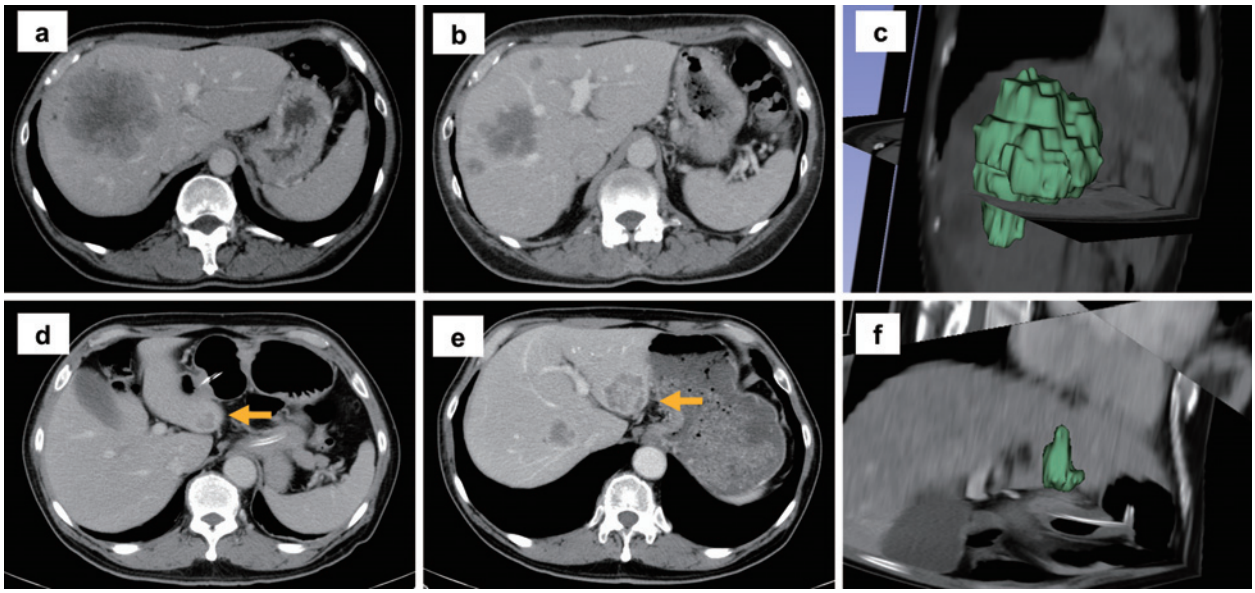

Figure 6. Representative cases.
Case 1: (a) Pretreatment CT scan showed extensive liver metastasis at the S8 segment. (b) Post-treatment CT scan showed a remarkable decrease in liver metastases after systemic chemotherapy. (c) A 3D-CT texture image of a representative liver tumor.
Case 2: (d) Pretreatment CT scan showed liver metastasis at the S2 segment (arrow). (e) A post-treatment CT scan revealed that the liver tumor increased in size, and the treatment response was classified as a progressive disease according to the RECIST criteria. (f) A 3D-CT texture image of a representative liver tumor.

to larger clinical settings. Future research should thus focus on developing and implementing automated segmentation techniques to improve the objectivity and efficiency of the procedure.

Our study is the first to demonstrate that machine learning-based CT texture analysis of liver metastases predicts responses to systemic chemotherapy in mCRC patients. Machine learning-based CT texture analysis showed high predictive accuracy in the validation cohort. This method may be used to predict chemotherapy efficacy in the future. Further clinical and technical validation of this texture analysis is needed to confirm our results.

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Conflicts of Interest

There are no conflicts of interest.

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Author Contributions

The study conception and design were performed by Yuji Miyamoto and Takehi Nakaura. Material preparation, data collection and analysis were performed by Yuji Miyamoto, Mayuko Ohuchi, and Katsuhiro Ogawa. The first draft of the manuscript was written by Yuji Miyamoto and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the institutional review board of Kumamoto University hospital (approval code, no. 2000).

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