Original Article

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Abstract

Background Metastatic liver cancer (MLC) is mostly caused by metastases from gastrointestinal tumors and other malignancies. Stereotactic body radiotherapy (SBRT) is an important local treatment modality; however, marked heterogeneity of liver tumors leads to substantial differences in patients' responses to radiotherapy, making the identification of populations most likely to benefit from radiotherapy a key clinical challenge. Radiomics can extract large numbers of quantifiable features from medical images and has significant advantages in tumor diagnosis and treatment, but existing studies are mostly based on diagnostic CT or MRI, which differ from radiotherapy simulation images in acquisition parameters and phases. Moreover, most studies focus on intratumoral features, with a lack of systematic comparison of peritumoral features. Objective To explore the value of intratumoral and peritumoral radiomics features based on simulation CT combined with clinical factors in predicting the short-term efficacy of radiotherapy for liver metastases. Methods A total of 120 patients with liver metastases who underwent radiotherapy at Liuzhou Hospital of Traditional Chinese Medicine from January 2018 to April 2025 were retrospectively collected and randomly divided into a training set (n=84) and a test set (n=36) at a ratio of 7:3. Multivariate Logistic regression analysis was used to screen independent clinical influencing factors. Radiomics features from intratumoral, peritumoral 3 mm, and 5 mm regions were extracted; the least absolute shrinkage and selection operator (LASSO) was used for feature selection, and a random forest (RF) algorithm was used to construct prediction models for the short-term efficacy of radiotherapy for liver metastases. Short-term efficacy was evaluated 3 months after radiotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Complete response and partial response were classified as radiosensitive, whereas stable disease and progressive disease were classified as radioresistant. The predictive performance and differences in performance among the models were evaluated using receiver operating characteristic (ROC) curves and the DeLong test. Results Multivariate Logistic regression analysis showed that the number of liver metastases was an independent influencing factor for short-term radiotherapy efficacy (OR=0.016, 95%CI=0.003~0.083, P<0.001). LASSO regression selected 5 radiomics features closely related to efficacy for model construction. The AUCs of the INTRA, Peri3mm, Peri5mm, IntraPeri5mm, IntraPeri3mm, and Clinic prediction models for predicting the short-term efficacy of radiotherapy for liver metastases were 0.767, 0.700, 0.689, 0.803, 0.828, and 0.783, respectively. The combined model (Combined) integrating IntraPeri3mm with Clinic had an AUC of 0.864, an accuracy of 0.889, a sensitivity of 0.833, and a specificity of 0.900. The DeLong test showed that the IntraPeri3mm model outperformed the single models (P<0.05). Conclusion CT-based intratumoral radiomics features combined with peritumoral 3 mm radiomics features and clinical factors can effectively predict the short-term efficacy of radiotherapy for liver metastases and have good potential for clinical translation.

Full Text

Original Article

Study on Short-Term Radiosensitivity of Liver Metastases after Radiotherapy Based on Intratumoral and Peritumoral Radiomics from Planning CT Combined with Clinical Features

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Abstract

Background Metastatic liver cancer (MLC) is mostly caused by metastasis from gastrointestinal tumors and other malignancies. Stereotactic body radiotherapy (SBRT) is an important local treatment modality for MLC. However, the heterogeneity of liver tumors leads to marked differences in radiotherapy response among patients, making the identification of patients most likely to benefit from radiotherapy a key clinical challenge. Radiomics can extract a large number of quantitative features from medical images and has significant advantages in tumor diagnosis and treatment. However, most existing studies are based on diagnostic CT or MRI, which differ from radiotherapy planning images in acquisition parameters and imaging phase. Moreover, most studies have focused on intratumoral features, with a lack of systematic comparison of peritumoral features.

Objective To explore the value of intratumoral and peritumoral radiomic features based on planning CT combined with clinical factors in predicting the short-term efficacy of radiotherapy for liver metastases.

Methods A total of 120 patients with liver metastases who received radiotherapy at Liuzhou Hospital of Traditional Chinese Medicine from January 2018 to April 2025 were retrospectively collected and randomly divided at a ratio

of 7:3 into a training set (n=84) and a test set (n=36). Multivariate Logistic regression analysis was used to screen independent clinical influencing factors. Radiomic features were extracted from the intratumoral region and the 3 mm and 5 mm peritumoral regions. The least absolute shrinkage and selection operator (LASSO) was used for feature selection, and a random forest (RF) algorithm was used to construct prediction models for the short-term efficacy of radiotherapy in liver metastases. Short-term efficacy was evaluated 3 months after completion of radiotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Complete response and partial response were classified as radiosensitive, while stable disease and progressive disease were classified as radioresistant. Receiver operating characteristic (ROC) curves and the DeLong test were used to evaluate the predictive performance of the models and differences in performance.

Results Multivariate Logistic regression analysis showed that the number of liver metastases was an independent factor influencing short-term radiotherapy efficacy (OR=0.016, 95%CI=0.003-0.083, P<0.001). LASSO regression selected 5 radiomic features closely associated with efficacy for construction of the prediction models. The AUCs of the INTRA, Peri3mm, Peri5mm, IntraPeri5mm, IntraPeri3mm, and Clinic prediction models for predicting the short-term efficacy of radiotherapy for liver metastases were 0.767, 0.700, 0.689, 0.803, 0.828, and 0.783, respectively. The combined model (Combined), integrating IntraPeri3mm with Clinic, had an AUC of 0.864, an accuracy of 0.889, a sensitivity of 0.833, and a specificity of 0.900. The DeLong test showed that the IntraPeri3mm model was superior to the single models (P<0.05).

Conclusion CT-based intratumoral radiomic features combined with 3 mm peritumoral radiomic features and integrated with clinical factors can effectively predict the short-term efficacy of radiotherapy for liver metastases and have good potential for clinical translation.

Keywords liver metastases; radiotherapy; radiomics; peritumoral region; prediction model

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An Exploratory Study on Short-term Radiosensitivity of Liver Metastases after Radiotherapy Based on Intratumoral and Peritumoral Radiomics from Planning CT Combined with Clinical Features

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【Abstract】 Background Metastatic liver cancer (MLC) is most commonly caused by metastasis from gastrointestinal tumors. Stereotactic body radiotherapy (SBRT) is an important local treatment modality; however, tumor heterogeneity in the liver leads to substantial variability in patient responses, making the identification of patients most likely to benefit from radiotherapy a critical clinical challenge. Radiomics enables the extraction of numerous quantifiable features from medical images and offers significant advantages in tumor diagnosis and treatment. However, most existing studies are based on diagnostic CT or MRI, which differ in acquisition parameters and timing from radiotherapy planning images. Moreover, most studies focus on intratumoral features, with a lack of systematic comparison involving peritumoral features. **Objective** To explore the value of combining intratumoral and peritumoral radiomic features derived from planning CT with clinical factors in predicting the short-term efficacy of radiotherapy for liver metastases. **Methods** A retrospective analysis was conducted on 120 patients with liver metastases who received radiotherapy at Liuzhou Traditional Chinese Medicine Hospital from January 2018 to April 2025. Patients were randomly divided into a training cohort (n = 84) and a test cohort (n = 36) at a 7 3 ratio. Multivariate Logistic regression analysis

was used to identify independent clinical factors. Radiomic features were extracted from the intratumoral region and peritumoral regions with 3 mm and 5 mm margins. Features were selected using the least absolute shrinkage and selection operator (LASSO) regression, and prediction models were constructed using the random forest (RF) algorithm. Short-term efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at three months post-radiotherapy; patients with complete response and partial response were classified as radiosensitive, while those with stable disease and progressive disease were classified as radioresistant. Model performance was assessed using receiver operating characteristic (ROC) curves and the DeLong test. **Results** Multivariate Logistic regression analysis identified the number of liver metastases as an independent factor affecting short-term radiotherapy response ($OR = 0.016$, $95\%CI = 0.003$–0.083, $P < 0.001$). LASSO regression selected five radiomic features strongly associated with efficacy for predictive model construction. The AUCs for predicting short-term radiotherapy efficacy of liver metastases were 0.767, 0.700, 0.689, 0.803, 0.828, and 0.783 for the INTRA, Peri3mm, Peri5mm, IntraPeri5mm, IntraPeri3mm, and Clinic models, respectively. The combined model (IntraPeri3mm–Clinic) achieved an AUC of 0.864, with an accuracy of 0.889, a sensitivity of 0.833, and a specificity of 0.900. Delong' s test indicated that the IntraPeri3mm model was superior to the single models ($P < 0.05$). **Conclusion** CT-based radiomic features integrating intratumoral and peritumoral (3 mm) regions, combined with clinical factors, can effectively predict the short-term response of liver metastases to radiotherapy, demonstrating promising potential for clinical translation.

【Key words】 Liver Metastases; Radiotherapy; Radiomics; Peritumoral Region; Predictive Model

Metastatic liver cancer (MLC) is a common complication of advanced malignant tumors. It is mainly caused by metastasis from gastrointestinal tumors, such as colorectal cancer and gastric cancer, while lung cancer, pancreatic cancer, and breast cancer are also important primary sources[1-2]. As an important local treatment modality for liver metastases, radiotherapy has been proven to be safe and effective, with a high local control rate and manageable toxicity[3-4]. However, the high heterogeneity of liver tumors leads to marked differences in patients' responses to radiotherapy[4-5]. How to identify the population most likely to benefit from radiotherapy has therefore become a key challenge in clinical practice[5-6]. Radiomics, as an emerging auxiliary diagnostic and therapeutic technology, can extract a large number of quantifiable features from medical images and has demonstrated significant advantages in tumor diagnosis, treatment decision-making, and prognostic evaluation[7-8].

In recent years, scholars in China and abroad have gradually applied radiomics to studies related to liver metastases[9-10]. At present, most radiomics studies are based on diagnostic CT or MRI. Although these images are clearly displayed, they differ spatially and in contrast from the images obtained when patients actually receive radiotherapy. By comparison, radiotherapy planning CT is used

directly to formulate treatment plans; the geometric position of the images is completely consistent with the treatment target volume, and thus it can better reflect tumor characteristics in the real radiotherapy setting. Existing radiomics studies of MLC are mostly limited to intratumoral features, while systematic exploration of the peritumoral region is insufficient, and the predictive performance of different peritumoral ranges remains unclear. Accordingly, this study innovatively uses radiotherapy planning CT images to construct a model incorporating intratumoral and peritumoral radiomic features together with clinical factors, with the aim of predicting short-term efficacy after radiotherapy for liver metastases. This is expected to achieve a direct transition from prediction based on diagnostic images to prediction based on treatment images, offering greater clinical operability and translational potential.

1 Materials and Methods

1.1 General Information

This study retrospectively included patients with liver metastases who received radiotherapy for liver tumors at Liuzhou Traditional Chinese Medicine Hospital from January 2018 to April 2025 and had complete follow-up data. All included patients with liver metastases were assessed by a multidisciplinary team (MDT) as unsuitable for radical surgical resection or local ablation therapy. The final treatment plan was determined after full communication with patients and their families and after informed consent was obtained. Inclusion criteria: (1) a clear diagnosis of liver metastasis: all patients were confirmed through MDT discussion. Some patients were pathologically confirmed by puncture biopsy, while the remaining patients were comprehensively diagnosed by the MDT on the basis of typical imaging findings, pathology of the primary lesion, and clinical course. (2) Completion of planning CT scanning suitable for delineation within 2 weeks before the start of radiotherapy. (3) Expected survival $ $3 months and completion of follow-up. Exclusion criteria: [[unclear: text continues beyond the bottom of the page, beginning with “资”]].

incomplete data, poor image quality, or failure to complete treatment follow-up. (4) During radiotherapy, no other local or systemic antitumor treatment targeting liver metastases was received. (5) At least one intrahepatic lesion was evaluable according to the modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1), and the normal liver volume

$$totallivervolumeminusgrosstumorvolume(GTV)$$

was >700 cm^3. This study was approved by the Medical Ethics Committee of Liuzhou Traditional Chinese Medical Hospital (approval No.: 2025-KY-XS-003-01), and the requirement for individual informed consent was waived.

A total of 120 samples were included in this study. According to short-term efficacy assessed by RECIST 1.1 criteria, complete response and partial response were classified as radiosensitive, whereas stable disease and progressive disease

were classified as radioresistant. Random sampling was performed at a ratio of 7:3. The training set contained 84 cases, including 27 radiosensitive cases and 57 radioresistant cases; the testing set contained 36 cases, including 6 radiosensitive cases and 30 radioresistant cases.

1.2 Data Extraction

Baseline clinical data of the patients were collected, including age, sex, Karnofsky Performance Status Score (KPS), primary tumor origin (colorectal cancer/non-colorectal cancer), number of liver metastases, GTV and planning target volume (PTV), total radiotherapy dose, fractional dose, number of fractions, and other variables. Primary lesion type (colorectal cancer/non-colorectal cancer) was included in the analysis as a binary categorical variable.

1.3 Radiotherapy Regimen

All included cases were discussed by an MDT before treatment, and individualized treatment plans were jointly formulated. The patient' s dose-fractionation pattern was comprehensively determined according to lesion location, number, size, organs at risk and their received doses, and tolerable positioning method. For patients with smaller lesions ($ $5 cm), lesions far from the gastrointestinal tract and central bile duct, and for whom 4D-CT simulation could be performed, SBRT with a single fraction dose greater than 5 Gy was adopted; for patients with large lesions or lesions adjacent to organs at risk, moderate-dose fractionation or conventional fractionation was used. Intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), or SBRT plans were designed on the basis of 6-MVX rays. Treatment plans were optimized using the Raystation or Eclips 13.5 software system. Optimized treatment regimens were formulated by reference to previous literature. For moderate-dose fractionation or conventional fractionation, the prescribed dose was 2–4 Gy/fraction, with 20–30 fractions; for SBRT, the prescribed dose was 5–6 Gy/fraction, with 8–10 fractions. It was required that 95% of the PTV reach the prescribed dose and that normal tissue dose limits remain within safe ranges[11].

Normal tissue dose constraints mainly included[12]: (1) SBRT: when normal liver volume was >700 mL, the mean normal liver dose was <15 Gy, or when liver volume was >800 mL, it was <18 Gy. The maximum doses to the stomach and small intestine should both be <22.2–35.0 Gy, preferably <30 Gy; the optimal esophageal dose was <32 Gy. The optimal mean dose to both kidneys was <10 Gy; the maximum spinal cord dose was <21.9–30.0 Gy, preferably <25 Gy. (2) Conventional fractionated radiotherapy: the mean normal liver dose was <23 Gy; maximum gastric dose $ $54 Gy, V50 <2%, and small-intestine V50 $ $10%–15%. The mean dose to both kidneys was $ $15 Gy; if the mean dose to one kidney was >19 Gy, the irradiated dose to the other kidney was minimized as much as possible; the maximum spinal cord dose was <40 Gy. Treatment was delivered using a Varian Trilogy or Elekta Synergy accelerator, with cone

beam CT (CBCT) guidance to ensure accuracy.

1.4 Follow-up and Outcome Measures

All patients entered regular follow-up after completion of radiotherapy. Short-term efficacy was evaluated at the first follow-up 3 months ($±$2 weeks) after radiotherapy using MRI and/or contrast-enhanced abdominal CT. Follow-up items included tumor markers, CT, MRI, and so forth. Clinical efficacy was evaluated according to RECIST 1.1 criteria, and local control within the radiotherapy field was assessed, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Evaluation criteria: (1) radioresistance: intrahepatic lesions within the radiotherapy field were evaluated as PD+SD 3 months after radiotherapy; (2) radiosensitivity: intrahepatic lesions within the radiotherapy field were evaluated as CR+PR 3 months after radiotherapy.

1.5 Acquisition, Preprocessing, Segmentation, and Radiomics Feature Extraction, Screening, and Dimensionality Reduction of Simulation CT Images

1.5.1 Image Acquisition

All patients underwent liver scanning on a Philips large-aperture CT simulator (Philips CT Big Bore RT). The scanning parameters were unified as follows: helical scanning mode, tube voltage 80–140 kVp, slice thickness 5 mm, matrix 512 × 512, tube current 150–540 mA, and standard reconstruction algorithm. Patients were imaged in the supine position during full inspiration, and the scanning range mainly included the entire liver. After non-contrast scanning, single-phase contrast-enhanced scanning was performed. Iohexol injection contrast agent (iodine concentration 350 g/L) was injected via the antecubital vein at a flow rate of 2.1–2.3 mL/s, with a dose of 90 mL, and images were acquired 50–60 s after the start of injection (portal venous phase). All radiomics features in this study were extracted on the basis of these portal venous phase enhanced images.

1.5.2 Image Preprocessing

To compensate for differences in voxel spacing and maintain grayscale consistency, images were resampled to a voxel spacing of $1 \times 1 \times 1$ mm^3 before delineation of the region of interest (ROI), and grayscale normalization was performed.

1.5.3 ROI Segmentation

Using ITK-snap 3.8 software on the simulation CT images, two attending radiation oncologists with more than 5 years of experience in abdominal tumor radiotherapy target delineation independently performed manual delineation

(segmentation) of the ROI for all tumors. For patients with multiple liver metastases, according to the radiotherapy plan, all target lesions intended to receive radiotherapy and with clearly definable boundaries were independently delineated. Subsequently, at the stage of radiomics feature extraction, features were extracted separately for each lesion. To predict efficacy at the patient level, the radiomics feature values of all target lesions in the same patient were weighted and averaged (with lesion volume as the weight), ultimately yielding a composite feature vector representing the patient' s overall tumor burden and radiomics features. For cases in which the delineation results of the two physicians were inconsistent (using a Dice similarity coefficient <0.85 as

···as the threshold for inconsistency), the case was submitted to a third chief physician with more than 10 years of experience for review and final adjudication, and the finally determined contour was taken as the standard.

1.5.4 Peritumoral-region expansion

To systematically investigate the contribution of the peritumoral region to prediction and to determine the optimal peritumoral analysis range, this study referred to previous research in fields such as liver cancer and breast cancer

, and selected 3 mm and 5 mm as representative peritumoral distances for analysis. Using the Simple ITK 3.6 package in Python, the intratumoral 3D-ROI was expanded in three-dimensional space at radial intervals of 1 mm to explore the influence of different peritumoral distances on the predictive accuracy of our model. To maximize the reliability and reproducibility of the peritumoral-region definition, after automatic expansion generated the initial annular peritumoral region, two radiation oncologists with more than 5 years of experience jointly reviewed the expanded regions of all cases slice by slice. Structures in the expanded region that clearly extended beyond the liver contour or mistakenly included adjacent large vessels, bile ducts, and tissues other than normal liver parenchyma were manually removed (Figure 1), ensuring that the extracted peritumoral radiomics features mainly reflected the microenvironment of the tumor–liver interface.

1.5.5 Feature extraction

The radiomics features extracted in this study covered three categories: geometric features, intensity features, and texture features. Based on PyRadiomics 3.6, seven classes of features were extracted from the intratumoral and peritumoral regions, including first-order statistics, gray level co-occurrence matrix (GLCM), gray-level dependence matrix, gray level run length matrix (GLRLM), gray level size zone matrix (GLSZM), neighborhood gray tone difference matrix (NGTDM), and shape features, with a total of 1,835 features per region; the intratumoral region combined with the 3 mm and 5 mm peritumoral regions generated 3,669 features, respectively.

1.5.6 Radiomics feature selection

Highly redundant features (correlation coefficient >0.9) were removed by Spearman rank-correlation analysis to reduce collinearity among features. Subsequently, the maximum relevance minimum redundancy (mRMR) algorithm was used to screen a subset of features that were highly correlated with treatment efficacy and had low redundancy with one another. Finally, least absolute shrinkage and selection operator (LASSO) regression combined with 10-fold cross-validation was used to select the optimal regularization parameter, further compress the number of features, and determine the coefficient weight of each feature. Radiomics features highly correlated with radiotherapy efficacy in patients with liver metastases were ultimately selected for subsequent model construction.

1.6 Model construction

Seven machine-learning algorithms were used to construct prediction models: logistic regression (LR), support vector machine (SVM), K-nearest neighbors algorithm (KNN), random forest, eXtreme Gradient Boosting (XGBoost), Extra Trees, and Light Gradient Boosting Machine (LightGMB). The construction process for all models was completed strictly within the training set: first, LASSO regression and Spearson correlation analysis were used to reduce the dimensionality of and screen radiomics features in the training set, yielding a set of key features; then, these key features were input into the random-forest algorithm for model training to generate the final prediction model. The flowchart is shown in Figure 2.

1.7 Statistical analysis

Data analysis was performed using R 4.5.2 software. Radiomics feature extraction was implemented with PyRadiomics 3.0.1, and machine-learning modeling was implemented with Scikit-learn 1.0.2. Quantitative data with a normal distribution were expressed as ($\bar{x}\pm s$), and between-group comparisons were performed using the independent-samples t-test. Quantitative data with a non-normal distribution were expressed as $M(P_{25}, P_{75})$, and between-group comparisons were performed using the Mann–Whitney test. Categorical variables were expressed as constituent ratios, and between-group comparisons were performed using the χ^2 test or Fisher' s exact test. Univariate and multivariate logistic regression were used to screen influencing factors for short-term radiotherapy efficacy. The predictive performance of the models was evaluated using receiver operating characteristic (ROC) curves; the area under the ROC curve (AUC), sensitivity, specificity, and accuracy were calculated; and the DeLong test and integrated discrimination improvement index were used to compare the eff···

Note: The red region represents the intratumoral region segmented by the oncologist, and the green annular regions indicate multiple peritumoral regions obtained through expansion.

Figure 1 Example masks at different expansion distances on the image

Figure 1 Examples of masks with different expansion distances on the image

···differences. A value of $P < 0.05$ was considered statistically significant.

2 Results

2.1 Comparison of baseline data between the training and test sets

A total of 120 patients with liver metastases were included in this study (491 lesions in total) and were randomly divided at a ratio of 7:3 into a training set (84 cases) and a test set (36 cases). The GTV and PTV of patients in the training set were higher than those in the test set, while the radiotherapy fractional dose, GTV minimum dose, GTV maximum dose, PTV minimum dose, and PTV maximum dose were lower than those in the test set; all differences were statistically significant ($P < 0.05$). The distributions of total radiotherapy dose, GTV mean dose, and PTV mean dose differed significantly between the two groups ($P < 0.05$). There were no statistically significant differences between the two groups in sex, age, number of metastases, KPS score, number of fractions, or primary tumor origin ($P > 0.05$), as shown in Table 1.

2.2 Comparison of clinical data between the radiotherapy-resistant and radiotherapy-sensitive groups in the training set

In the training set, the number of metastases (proportion with ≥ 4 metastases) and total radiotherapy dose in the radiotherapy-resistant group were higher than those in the radiotherapy-sensitive group, and the differences were statistically significant ($P < 0.05$). There were no statistically significant differences between the radiotherapy-resistant and radiotherapy-sensitive groups in sex, age, KPS score, GTV, GTV minimum dose, GTV maximum dose, GTV mean dose, radiotherapy fractional dose, number of fractions, PTV, PTV minimum dose, PTV maximum dose, PTV mean dose, or primary tumor origin ($P > 0.05$), as shown in Table 2.

2.3 Evaluation of short-term efficacy

According to RECIST 1.1 criteria, treatment efficacy was evaluated 3 months after radiotherapy. The results showed 1 case of CR (0.8%), 32 cases of PR (26.6%), 65 cases of SD (54.1%), and 22 cases of PD (18.3%).

2.4 Multivariate Logistic regression analysis of factors influencing short-term radiotherapy efficacy

Short-term radiotherapy efficacy (assigned values: radiotherapy resistance = 0, radiotherapy sensitivity = 1) was used as the dependent variable, while the number of liver metastases, KPS score, number of radiotherapy fractions, age, radiotherapy fractional dose, PTV minimum dose, total radiotherapy dose, PTV

mean dose, GTV maximum dose, GTV minimum dose, and GTV mean dose (all assigned as measured values) were used as independent variables for multivariate Logistic regression analysis. The results showed that the number of liver metastases ($OR = 0.016$, $95\%CI = 0.003 \sim 0.083$, $P < 0.001$) was an independent influencing factor for short-term radiotherapy efficacy, as shown in Table 3.

2.5 Evaluation of model diagnostic performance

The indicator that was statistically significant in the multivariate Logistic regression analysis (number of liver metastases) was included to construct a Clinic (clinical model) for predicting short-term radiotherapy efficacy. Meanwhile, radiomics features were used to construct the INTRA (intratumoral), Peri3mm (peritumoral 3 mm), Peri5mm (peritumoral 5 mm), IntraPeri3mm (intratumoral + peritumoral 3 mm), IntraPeri5mm (intratumoral + peritumoral 5 mm), and Combined (intratumoral + peritumoral 3 mm + clinical model) models, and ROC curves were plotted for each model. The AUCs for predicting radiotherapy efficacy were as follows: INTRA model, 0.767 ($95\%CI = 0.555 \sim 0.978$); Peri3mm model, 0.700 ($95\%CI = 0.447 \sim 0.953$); Peri5mm model, 0.689 ($95\%CI = 0.414 \sim 0.964$); IntraPeri5mm mo–

Figure 2 Flowchart of predictive model construction

Visible labels in the flowchart: liver metastases; images; manual ROI delineation; peritumoral ROI expansion; feature weights; LASSO regression; feature statistics; feature ratios; prediction histogram; model ROC curve; cohort training and DeLong test; clinical application.

model was 0.803 (95% CI=0.646-0.960), the IntraPeri3mm model was 0.828 (95% CI=0.658-0.998), the Clinic model was 0.783 (95% CI=0.601-0.965), and the Combined model was 0.864 (95% CI=0.681-1.000), as shown in Table 4 and Figure 3.

The DeLong test results showed that the AUC of the IntraPeri3mm model was higher than those of the Peri3mm, Peri5mm, and Clinic models ($P<0.05$). In contrast, when INTRA was compared with the IntraPeri3mm model, and when IntraPeri5mm was compared with the IntraPeri3mm and Combined models, the differences were not statistically significant.

Table 1 Comparison of baseline data between the training set and the validation set

Group	Cases	Sex: male [cases (%)]	Sex: female [cases (%)]	Age [$M(P_{25}, P_{75})$, $years$]	Number of metastases: 1–3 [cases (%)]	Number of metastases: $ $4 [cases (%)]	KPS: <80 [cases (%)]	KPS: $ $80 [cases (%)]	GTV [$M(P_{25}, P_{75})$, cm^3]
Test set	36	23 (63.89)	13 (36.11)	61.0 (47.0, 69.0)	13 (36.11)	23 (63.89)	6 (16.67)	30 (83.33)	40.21 (11.66, 91.77)
Training set	84	51 (60.71)	33 (39.29)	66.0 (57.0, 73.0)	30 (35.71)	54 (64.29)	23 (27.38)	61 (72.62)	109.85 (34.87, 300.28)
Test statistic value		0.015b	0.015b	−1.780	0b	0b	1.048b	1.048b	−2.775
P value		0.902	0.902	0.075	1.000	1.000	0.306	0.306	0.006

Group	GTV minimum dose [$M(P_{25}, P_{75})$, cGy]	GTV maximum dose [$M(P_{25}, P_{75})$, cGy]	GTV mean dose [$M(P_{25}, P_{75})$, cGy]	Total radiotherapy dose [$M(P_{25}, P_{75})$, cGy]	Radiotherapy fraction dose [$M(P_{25}, P_{75})$, cGy]	Number of fractions [$M(P_{25}, P_{75})$, $times$]
Test set	5 046.75(4 955.12, 5 966.63)	5 723.60(5 544.37, 6 542.13)	5 300.55(5 246.30, 6 225.10)	5 040.00(5 040.00, 6 000.00)	190.00(180.00, 200.00)	28.00(28.00, 30.00)
Training set	4 929.90(4 008.03, 5 406.47)	5 624.15(5 352.70, 5 887.70)	5 285.10(4 736.25, 5 660.57)	5 040.00(4 875.00, 5 400.00)	180.00(180.00, 200.00)	28.00(25.00, 30.00)
Test statistic value	−2.674	−2.010	−1.801	−1.989	−2.136	−1.221
P value	0.007	0.044	0.072	0.047	0.033	0.222

Group	PTV [$M(P_{25}, P_{75}), cm^3$]	PTV minimum dose [$M(P_{25}, P_{75}), cGy$]	PTV maximum dose [$M(P_{25}, P_{75}), cGy$]	PTV mean dose [$M(P_{25}, P_{75}), cGy$]	Primary lung tumor origin: rectal cancer [cases (%)]	Primary lung tumor origin: non-rectal cancer [cases (%)]
Test set	113.27 (55.10, 283.02)	4 504.85 (4 003.65, 5 092.32)	5 747.70 (5 597.10, 6 557.12)	5 278.65 (5 231.55, 6 182.65)	19 (52.78)	17 (47.22)
Training set	205.82 (77.11, 457.16)	3 736.20 (2 648.85, 4 701.40)	5 667.10 (5 396.42, 6 012.20)	5 250.00 (4 697.20, 5 584.52)	41 (48.81)	43 (51.19)
Test statistic value	−2.004	−2.674	−2.056	−2.400	0.04b	0.04b
P value	0.045	0.007	0.040	0.016	0.842	0.842

Note: a indicates a t value; b indicates a χ^2 value; the remaining test statistic values are Z values. KPS = Karnofsky performance status score; GTV = gross tumor volume; PTV = planning target volume.

Table 2 Comparison of baseline data between radiotherapy-resistant and radiotherapy-sensitive groups in the training set

Group	Cases	Sex: male [cases (%)]	Sex: female [cases (%)]	Age [$M(P_{25}, P_{75}), years$]	Number of metastases: 1–3 [cases (%)]	Number of metastases: ≥4 [cases (%)]	KPS: <80 [cases (%)]	KPS: ≥80 [cases (%)]	GTV [$M(P_{25}, P_{75}), cm^3$]
Radiotherapy-resistant group	57	35 (61.404)	22 (38.596)	64.5 ± 12.0	11 (19.298)	46 (80.702)	17 (29.825)	40 (70.175)	109.700 (31.770, 269.795)
Radiotherapy-sensitive group	27	16 (59.259)	11 (40.741)	64.9 ± 11.5	19 (70.370)	8 (29.630)	6 (22.222)	21 (77.778)	119.570 (47.670, 383.775)

Group	Cases	Sex: male [cases (%)]	Sex: female [cases (%)]	Age [$M(P_{25}, P_{75})$, $years$]	Number of metastases: 1–3 [cases (%)]	Number of metastases: $ $4 [cases (%)]	KPS: <80 [cases (%)]	KPS: $ $80 [cases (%)]	GTV [$M(P_{25}, P_{75})$, cm^3]
Test statistic value		0b	0b	−0.166a	18.65b	18.65b	0.219b	0.219b	−0.862
P value		>0.999	>0.999	0.869	<0.001	<0.001	0.640	0.640	0.389

Group	Cases	GTV minimum dose [$M(P_{25}, P_{75})$, cGy]	GTV maximum dose [$M(P_{25}, P_{75})$, cGy]	GTV mean dose [$M(P_{25}, P_{75})$, cGy]	Total radiotherapy dose [$M(P_{25}, P_{75})$, cGy]	Radiotherapy fraction dose [$M(P_{25}, P_{75})$, cGy]	Number of fractions [$M(P_{25}, P_{75})$, $times$]
Radiotherapy-resistant group	4	943.200(4 169.000, 5 692.000)	5 639.900(5 479.100, 6 123.100)	5 292.100(5 221.100, 6 117.000)	5 040.000(5 000.000, 5 940.000)	180.000(180.000, 200.000)	28.000(28.000, 30.000)
Radiotherapy-sensitive group	4	725.200(3 083.500, 5 026.600)	5 546.100(4 980.000, 5 778.750)	5 275.400(4 679.200, 5 327.050)	5 040.000(4 500.000, 5 040.000)	180.000(180.000, 200.000)	28.000(25.000, 28.000)
Test statistic value		−1.465	−1.111	−1.236	−2.068	−0.793	−1.904
P value		0.143	0.267	0.217	0.039	0.428	0.057

Group	PTV [$M(P_{25}, P_{75})$, $Mdn(P_{25}, P_{75})$, MCD]	PTV minimum dose [$M(P_{25}, P_{75})$, $Mdn(P_{25}, P_{75})$, MCD]	PTV maximum dose [$M(P_{25}, P_{75})$, $Mdn(P_{25}, P_{75})$, MCD]	PTV mean dose [$M(P_{25}, P_{75})$, $Mdn(P_{25}, P_{75})$, cGy]	Primary lung tumor origin: rectal cancer [cases (%)]	Primary lung tumor origin: non-rectal cancer [cases (%)]
Radiotherapy-resistant group	189.630 (77.560, 398.270)	3 764.395 ± 1 566.288	5 673.100 (5 535.900, 6 123.100)	5 252.400 (5 095.200, 5 845.000)	29 (50.877)	28 (49.123)
Radiotherapy-sensitive group	222.798 (88.114, 678.305)	3 269.756 ± 1 596.619	5 618.300 (5 011.150, 5 809.700)	5 212.500 (4 659.600, 5 293.900)	12 (44.444)	15 (55.556)
Test statistic value	−0.441	1.334a	−1.044	−1.283	0.101b	0.101b
P value	0.660	0.188	0.296	0.199	0.751	0.751

Note: a indicates a t value; b indicates a χ^2 value; the remaining test statistic values are Z values.

A. ROC curve for the training-set radiomics models.
Y-axis: Sensitivity. *X-axis:* 1− Specificity.

- INTRA AUC: 0.874 (95% CI 0.799–0.950)
- Peri3mm AUC: 0.768 (95% CI 0.654–0.882)
- Peri5mm AUC: 0.829 (95% CI 0.741–0.917)
- IntraPeri3mm AUC: 0.911 (95% CI 0.850–0.972)
- IntraPeri5mm AUC: 0.928 (95% CI 0.866–0.989)
- Clinic AUC: 0.755 (95% CI 0.654–0.857)

B. ROC curve for the test-set radiomics models.
Y-axis: Sensitivity. *X-axis:* 1− Specificity.

- INTRA AUC: 0.767 (95% CI 0.555–0.978)
- Peri3mm AUC: 0.700 (95% CI 0.447–0.953)

- Peri5mm AUC: 0.689 (95% CI 0.414–0.964)
- IntraPeri3mm AUC: 0.828 (95% CI 0.658–0.998)
- IntraPeri5mm AUC: 0.803 (95% CI 0.646–0.960)
- Clinic AUC: 0.783 (95% CI 0.601–0.965)

C. ROC curve for the model combining the optimal training-set radiomics model with the clinical model.
Y-axis: Sensitivity. *X-axis:* 1− Specificity.

- Clinic AUC: 0.755 (95% CI 0.654–0.857)
- IntraPeri3mm AUC: 0.911 (95% CI 0.850–0.972)
- Combined AUC: 0.922 (95% CI 0.862–0.982)

D. ROC curve for the model combining the optimal test-set radiomics model with the clinical model.
Y-axis: Sensitivity. *X-axis:* 1− Specificity.

- Clinic AUC: 0.783 (95% CI 0.601–0.965)
- IntraPeri3mm AUC: 0.828 (95% CI 0.658–0.998)
- Combined AUC: 0.864 (95% CI 0.681–1.000)

Note: A shows the ROC curve of the training-set radiomics model; B shows the ROC curve of the test-set radiomics model; C shows the ROC curve of the model combining the optimal training-set radiomics model with the clinical model; D shows the ROC curve of the model combining the optimal test-set radiomics model with the clinical model. Clinic = clinical model; INTRA = intratumoral; Peri3mm = peritumoral 3 mm; Peri5mm = peritumoral 5 mm; IntraPeri3mm = intratumoral and peritumoral 3 mm; IntraPeri5mm = intratumoral and peritumoral 5 mm; Combined = intratumoral and peritumoral 3 mm + Clinic.

Figure 3 The ROC curves of each model for predicting the short-term therapeutic efficacy of radiotherapy

Table 3 Multivariate Logistic regression analysis of factors affecting the efficacy of recent radiotherapy

Variable	β	SE	Wald χ^2 value	P value	OR (95% CI)
Number of liver metastases	−4.135	0.847	23.84	<0.001	0.016 (0.003-0.083)
KPS	−0.131	0.720	0.03	0.879	0.877 (0.214-3.600)

Variable	β	SE	Wald χ^2 value	P value	OR (95% CI)
Number of radiotherapy fractions	0.310	0.296	1.10	0.379	1.364 (0.763–2.438)
Age	0.018	0.024	0.56	0.527	1.018 (0.972–1.066)
Radiotherapy fraction dose	0.095	0.049	3.86	0.099	1.100 (1.000–1.209)
PTV minimum dose	0.000	0.001	0.00	0.512	1.000 (0.999–1.001)
Total radiotherapy dose	−0.007	0.004	3.84	0.097	0.993 (0.986–1.000)
PTV mean dose	−0.005	0.004	1.94	0.254	0.995 (0.988–1.002)
GTV maximum dose	0.006	0.003	3.87	0.108	1.006 (1.000–1.012)
GTV minimum dose	0.000	0.001	0.00	0.947	1.000 (0.999–1.001)
GTV mean dose	0.003	0.004	0.50	0.601	1.003 (0.995–1.010)

Table 4 The performance evaluation results of radiotherapy efficacy predicted by each prediction model

Model	AUC	95% CI	Accuracy	Sensitivity	Specificity
INTRA	0.767	0.555–0.978	0.667	0.833	0.633
Peri3mm	0.700	0.447–0.953	0.861	0.333	0.967
Peri5mm	0.689	0.414–0.964	0.694	0.667	0.700

Model	AUC	95% CI	Accuracy	Sensitivity	Specificity
Intra Peri5mm	0.803	0.646–0.960	0.778	1.000	0.633
Intra Peri3mm	0.828	0.658–0.998	0.694	0.833	0.767
Clinic	0.783	0.601–0.965	0.750	0.833	0.733
Combined	0.864	0.681–1.000	0.889	0.833	0.900

Note: INTRA = intratumoral; Peri3mm = peritumoral 3 mm; Peri5mm = peritumoral 5 mm; IntraPeri3mm = intratumoral and peritumoral 3 mm; IntraPeri5mm = intratumoral and peritumoral 5 mm; Clinic = clinical model; Combined = intratumoral and peritumoral 3 mm + Clinic.

was not statistically significant ($P > 0.05$), as shown in Table 5.

Table 5 Comparison results of AUC for different imaging-based models and clinical models in predicting the short-term efficacy of radiotherapy

Model	Z value	P value
INTRA vs. IntraPeri3mm	1.31	0.192
Peri3mm vs. IntraPeri3mm	2.30	0.022
Peri5mm vs. IntraPeri3mm	2.81	0.005
IntraPeri5mm vs. IntraPeri3mm	1.78	0.076
Clinic vs. IntraPeri3mm	2.81	0.005
Combined vs. IntraPeri3mm	0.58	0.559

3 Discussion

Radiomics can extract high-throughput quantitative features from medical images, and can compensate for the limitations of traditional visual assessment in a noninvasive and objective manner, demonstrating important value in tumor diagnosis, treatment decision-making, and prognostic evaluation [13–15]. In recent years, this technology has been gradually applied in studies of liver metastases, but previous studies have mostly focused on intratumoral features, with insufficient exploration of microenvironmental information in the peritumoral region. Given that the peritumoral area serves as the tumor–host interface and contains prognostic information, this study aimed to systematically compare the predictive performance of intratumoral and different ranges of peritumoral radiomic features in liver metastases, and to integrate clinical parameters to construct a combined prediction model, thereby validating the predictive potential of radiomics based on planning CT for short-term radiotherapy efficacy.

The results showed that the peritumoral 3 mm (Peri3mm) model was superior to the peritumoral 5 mm (Peri5mm) model. This finding is consistent with the concept of "peritumoral radiomics" proposed by Liu et al. [16], and this study

extends it for the first time to the field of radiotherapy for liver metastases, identifying "peritumoral 3 mm" as the optimal boundary. The biological basis is that the 3 mm peritumoral region can best reflect the tumor-host interface microenvironment, such as inflammatory infiltration, neovascularization, and fibrosis, which directly affects radiosensitivity [17]. This study found that the intratumoral combined with peritumoral 3 mm (IntraPeri3mm) model had the best performance in predicting radiotherapy efficacy for liver metastases, with a test-set AUC of 0.828 (95%CI=0.658-0.998), outperforming single models using only intratumoral or only peritumoral features. In addition, multivariable Logistic regression analysis of clinical factors confirmed that the number of liver metastases was an independent predictor, which differs from the findings of domestic scholars. Their multivariable analysis of 39 patients with liver metastases showed that only radiotherapy dose and chemotherapy were independent prognostic factors, whereas the number of liver metastases was not included in the multivariable model [18]. This discrepancy may be due to the larger sample size in the present study, the use of modern precision radiotherapy techniques, and the use of short-term local control as the outcome indicator. After further integrating the number of liver metastases with IntraPeri3mm radiomic features, the AUC of the Combined model increased to 0.864 (95%CI=0.681-1.000), with an accuracy of 88.9, indicating that multimodal information is complementary and can effectively improve predictive performance.

At present, although there are theoretical differences in radiosensitivity among different tumors, the predictive weight of this variable was not high in the multivariable analysis of this study. We speculate that this may be related to the fact that the intratumoral and peritumoral radiomic features extracted from radiotherapy planning CT successfully captured a common imaging phenotype that is "cross-tumor type" and related to local radioresistance or radiosensitivity, such as tumor hypoxia, necrosis, and microenvironmental status. This phenotype is directly associated with the essence of local radioresistance/sensitivity, and its predictive ability surpasses the traditional assessment model that relies solely on the pathological type of the primary tumor. This finding confirms the core advantage of radiomics in "mining biological commonalities from imaging phenotypes," and provides a new perspective for understanding the general mechanisms of radiotherapy response.

The results of this study correspond with existing radiomics studies in the field of liver tumors. Previous studies have confirmed that CT-based radiomic features are valuable for prognostic assessment and prediction of radiotherapy efficacy in hepatocellular carcinoma (Hepatocellular Carcinoma, HCC) [19]. In the field of prognostic research on liver metastases, Hu et al. used CT radiomics to establish an automated model to predict progression-free survival in colorectal cancer liver metastases (Colorectal Cancer Liver Metastases, CRLM) [20]. However, that study focused on long-term prognosis, and differed from the present study in terms of study endpoint, target population, and model-building strategy; moreover, it focused only on the intratumoral region. Our work further expands the application scenarios of radiomics, suggesting that the intratumoral and

peritumoral heterogeneity information captured by radiomics may compensate for the insufficiency of traditional clinicopathological markers, providing a new dimension for accurate prediction of short-term efficacy. This is consistent with recent emphases on the therapeutic and prognostic value of the peritumoral region in oncology [21–23].

This study is intended for use before radiotherapy implementation, predicting the efficacy of radiotherapy for liver metastases in patients with liver metastases based on radiomics features from radiotherapy planning CT. Limitations include: (1) the single-center retrospective design may have selection bias; (2) the sample size was limited, and the conclusions need to be validated in multicenter studies with large samples; and (3) the biological mechanisms underlying the radiomic features still require further exploration in combination with pathology and genomics.

In summary, this study systematically compared, for the first time, the predictive performance of intratumoral and different ranges of peritumoral radiomic features in liver metastases, identified "peritumoral 3 mm"as the optimal boundary, and constructed an efficient combined model, providing new ideas for predicting radiotherapy efficacy in liver metastases and for individualized treatment. In the future, multicenter, large-sample prospective studies are needed to validate the model' s generalizability and promote its clinical translation.

Author contributions: Shang Wenyan was responsible for the conception and design of the study, implementation of the study, and drafting of the manuscript; Long Die performed data collection and organization, statistical processing, and preparation and presentation of figures and tables; Si Tao and Chen Haihui proposed the main research objectives, were responsible for manuscript revision, took overall responsibility for the article, and supervised and managed the work.

The authors declare no conflicts of interest.

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