



# MRI Radiomics Predicts Early Biological Progression in a Preclinical Colon Cancer Model Following Mesenchymal Stem Cell Intervention

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**Background:** Stem cell therapy is a potential approach for tumor treatment; however, its efficacy and safety remain incompletely controllable. Therefore, early prediction of tumor progression and therapeutic evaluation post-treatment to guide timely therapeutic adjustments is essential. Radiomics has recently been widely applied to assess tumor behavior and characteristics. This study aims to investigate the predictive value of MRI radiomics for therapeutic outcomes in the early stages of stem cell intervention in colon cancer.

**Methods:** Subcutaneous tumor models were established by implanting CM38 colon cancer cells into the inguinal region of C57BL/6 mice. Bone marrow mesenchymal stem cells (MSCs) were intravenously injected via the tail vein within 24 hours. T1 weighted MRI scans were performed on day 7 to extract radiomic features, monitor tumor growth, and evaluate neovascularization (CD34) and proliferation (Ki67) via immunohistochemistry. An early-stage MRI radiomics model was constructed to predict colon cancer progression.

**Results:** Tumors in the stem cell intervention group exhibited faster growth compared to the control group, though no significant volume difference was observed in the early phase. A total of 1162 radiomic features were extracted, with 17 strongly associated features (including texture features, first-order features texture and shape features) selected to build the prediction model. The final model demonstrated an AUC > 0.8 across both training and testing datasets.

**Conclusion:** Intravenous MSC injection promotes the progression of subcutaneously implanted CM38 colon cancer. An MRI radiomics-based predictive model was successfully established, enabling early prediction of tumor progression post-intervention.

**Keywords:** mesenchymal stem cells, radiomics predictive model, tumor microenvironment, magnetic resonance imaging, colon cancer

## Introduction

Mesenchymal stem cells (MSCs) exhibit tumor-homing properties and modulate tumor microenvironments by regulating immune components and suppressing inflammatory responses, thereby exerting antitumor effects.<sup>1-4</sup> Ghannam et al<sup>5</sup> demonstrated that MSCs inhibit T-cell proliferation and alleviate inflammation, while Sabine François et al<sup>6</sup> reported that intravenous MSC administration prolongs survival in carcinogen-exposed rats by reducing tumor incidence and delaying progression. However, the biosafety of MSCs requires critical attention. MSCs possess multidifferentiation potential, and their tumorigenic risks remain under investigation.<sup>7</sup> Additionally, MSCs secrete paracrine factors (eg, chemokines, cytokines, and growth factors) that may promote tumor progression and metastasis. For example, MSC-derived IL-6 and IL-8 enhance the malignant potential of colon and breast cancers.<sup>8</sup> Engineered MSCs have also been explored as drug delivery vehicles for targeted tumor therapy.<sup>9</sup> However, prolonged in vitro culture during engineering processes may lead to cellular enlargement, senescence, or contamination, potentially reducing tumor-homing efficiency or increasing carcinogenic risks.<sup>7</sup> Thus, the efficacy and safety of MSC-based therapies for colorectal cancer remain uncertain, necessitating early prediction of tumor progression to guide timely therapeutic adjustments.

Medical imaging serves as a cornerstone for tumor evaluation, enabling not only size measurement but also characterization of intratumoral features (eg, necrosis, hemorrhage, and invasion). Advanced MRI sequences, such as functional MRI (fMRI) and chemical exchange saturation transfer (CEST), provide insights into molecular alterations within tumor microenvironments. Studies by Kudo M and Niek Wijnen et al demonstrated that APTw imaging predicts Ki-67 expression in gliomas, meningiomas, and breast cancers,<sup>10–14</sup> likely reflecting proliferative activity and extracellular components in high-grade tumors.<sup>15</sup> However, these subtle differences are often imperceptible on conventional imaging. Radiomics offers a solution by enabling high-throughput extraction of quantitative features to detect microstructural variations.

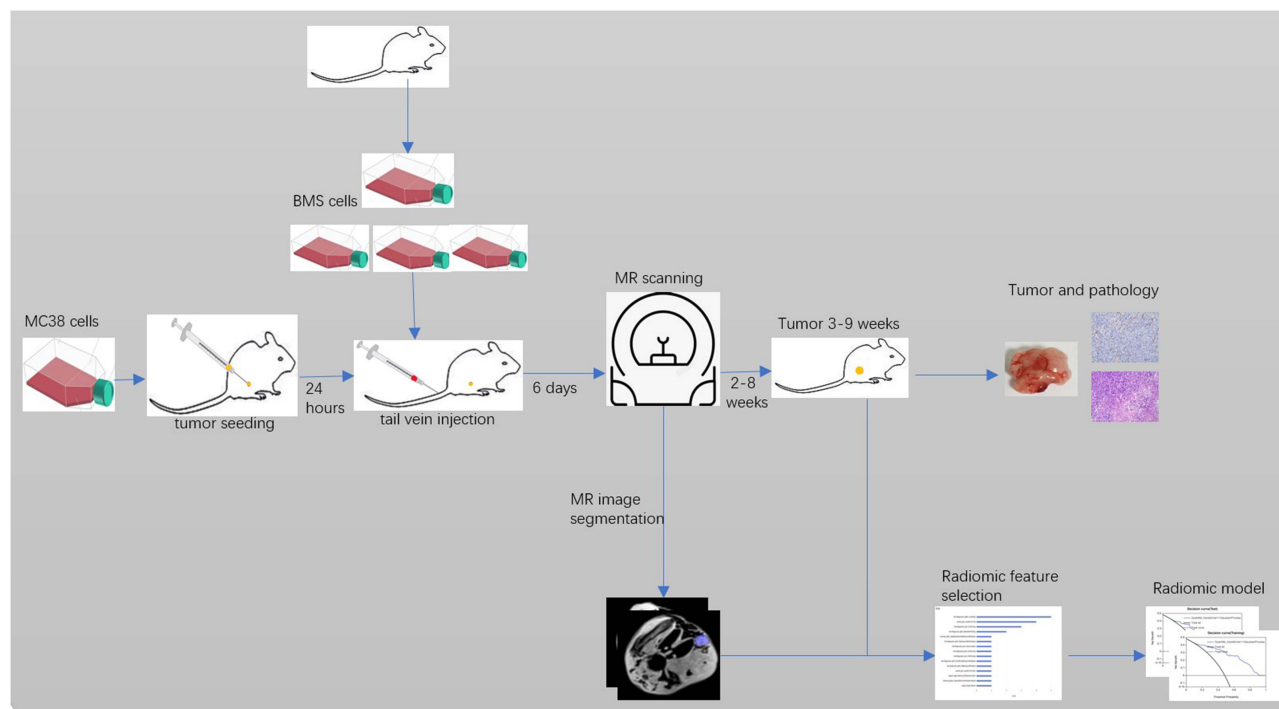
Recent advances highlight radiomics' role in noninvasive tumor characterization, genotyping, and survival prediction<sup>16,17</sup>. Johannes Müller et al correlated MRI texture features with hypoxic tumor microenvironments,<sup>18</sup> while Roger Sun and Michal R Tomaszewski et al<sup>16,19</sup> identified baseline CT radiomic features as predictors of PD-L1 immunotherapy response. MR-based radiomics has also been applied to predict tumor heterogeneity,<sup>20</sup> survival in gliomas,<sup>21</sup> and chemotherapy response in colorectal cancer metastases.<sup>22</sup>

Despite these advancements, it remains unclear whether radiomic features can detect early, subclinical tumor promoting effects of MSC therapy in colon cancer models. We hypothesize that MRI-based radiomics can non-invasively capture early biological changes such as increased neovascularization associated with MSC-induced tumor progression, before changes in tumor volume are apparent. Thus, MRI-based radiomics can serve as a non-invasive early treatment assessment to identify malignant responses as early as possible, offering more time for adjusting tumor treatment plans. This study leverages early-phase MRI radiomic features to monitor tumor progression and establish a predictive model, aiming to enable early intervention based on initial imaging data (Figure 1).

## Materials and Methods

### Ethics Statement

All animals were purchased from Hunan Laboratory Animal Co., Ltd. The animal experiments were approved by the Key Laboratory of Chongqing University Affiliated Central Hospital and conducted in accordance with the principles outlined by the Institutional Animal Care and Use Committee (IACUC).



**Figure 1** The wiring diagram of the article.

## Cells

Bone marrow mesenchymal stem cells (MSCs) were isolated from 1- to 7-day-old neonatal mice purchased from Hunan Laboratory Animal Co., Ltd. Bone marrow was extracted, and adherent cells were obtained after 48 hours of culture (with 37°C, 5% CO<sub>2</sub>, and 10% fetal bovine serum) by removing non-adherent cells. The adherent cells were expanded and passaged to passage 3 (P3) for subsequent experiments. Flow cytometry detected the surface markers (CD29, CD44, CD11b, CD45, BD Biosciences) expression of MSCs. A total of 10<sup>6</sup> CM38 cells (suspended in 100 μL phosphate buffered saline, PBS) were injected into the right inguinal region of the mice, followed by intravenous injection of 5 × 10<sup>5</sup> P3 MSCs (suspended in 100ul phosphate buffered saline) via the tail vein 12 hours later. Sixty mice were implanted with tumors, and one tumor was implanted in each mouse. The control group was injected with 100 μL PBS, while the intervention group was injected with 100 μL of mesenchymal stem cell suspension. There were 30 mice in each group.

## Imaging

Magnetic resonance imaging (MRI) was performed 7 days post-tumor implantation. Mice were anesthetized with isoflurane (4–5% for induction; 1–2% for maintenance) and scanned using a 3.0T MRI system (Siemens MAGNETOM Prisma) with a dedicated small animal coil. Imaging parameters included: TE 5.6 ms, TR 12.7 ms, FOV 64 mm × 64 mm, slice thickness 0.5 mm, and interslice gap 1 mm. Thermal insulation was maintained during scanning by wrapping mice in cotton pads.

## Tumor Growth

Tumor volume was recorded every 48 hours starting one week post-implantation. Tumor size was measured every 2 days using calipers, tumor volume (V) = (1/2) × length (L) × width (W) × height (H). Mice were euthanized via cervical dislocation under anesthesia when the tumor maximal diameter reached 15 mm–20 mm, and tumor tissues were harvested for subsequent analysis.

## Hematoxylin-Eosin (HE) and Immunohistochemical

Excised tumor tissues were fixed in 4% phosphate-buffered formalin, paraffin-embedded, and sectioned into 3 μm continuous slices. HE staining was performed for histological examination. Immunohistochemistry (IHC) was conducted to assess CD34 (Beyotime) and Ki67 (HUABIO) expression. Stained images were analyzed using ImageJ software (National Institutes of Health, USA) to quantify expression rates. Independent sample *t*-test was used for comparison between the two groups of data, and a P value < 0.05 was considered statistically significant.

## Radiomics Feature Extraction

T1WI images were selected for feature extraction. All regions of interest (ROIs) were delineated around the tumor boundaries using the Unified Imaging Intelligent One Stop Research Platform (uAI Research Portal, V20230515, <https://urp.united-imaging.com/>). Two radiologists with over 10 years of experience independently evaluated T1WI without knowledge of clinical outcomes. Automatically extracted radiomics features from each ROI, a total of 1162 image features were extracted, including shape features, firstorder features, and texture features.

## Feature Selection and Models Building

A random seed of 20 was used to split the data into groups for the 5-fold cross-validation. Before feature selection, the Z-score normalization was used to standardize all the extracted radiomics features. We applied intraclass coefficient (ICC) analysis to test the consistency of features extracted from two radiologists, and features with an ICC > 0.75 were selected for further analysis. Subsequently, Use K-best to select 300 image features with the highest correlation. Finally, we applied the least absolute shrinkage and selection operator (LASSO) method to select the most powerful features in the training set.

We implemented six different machine learning algorithms on the training dataset, including Gaussian Process (GP), Logistic Regression (LR), Quadratic Discriminant Analysis (QDA), Random Forest (RF), Random Gradient Descent (RGD), and Support Vector Machine (SVM). For each model, receiver operating characteristic (ROC) curves and the average area under the curve (AUC) were used to evaluate predictive performance.

Intraclass correlation coefficients (ICCs) from a two-way random effects model were used to assess interreader agreement for measuring ROI. The RS for prediction of treatment groups was constructed using LASSO statistics. The penalty parameter ( $\lambda$ ) was selected by 5-fold cross-validation and minimization of the cross-validation function. Independent sample *t*-test was used to compare the tumor volume between the two groups.  $p < 0.05$  were considered significant.

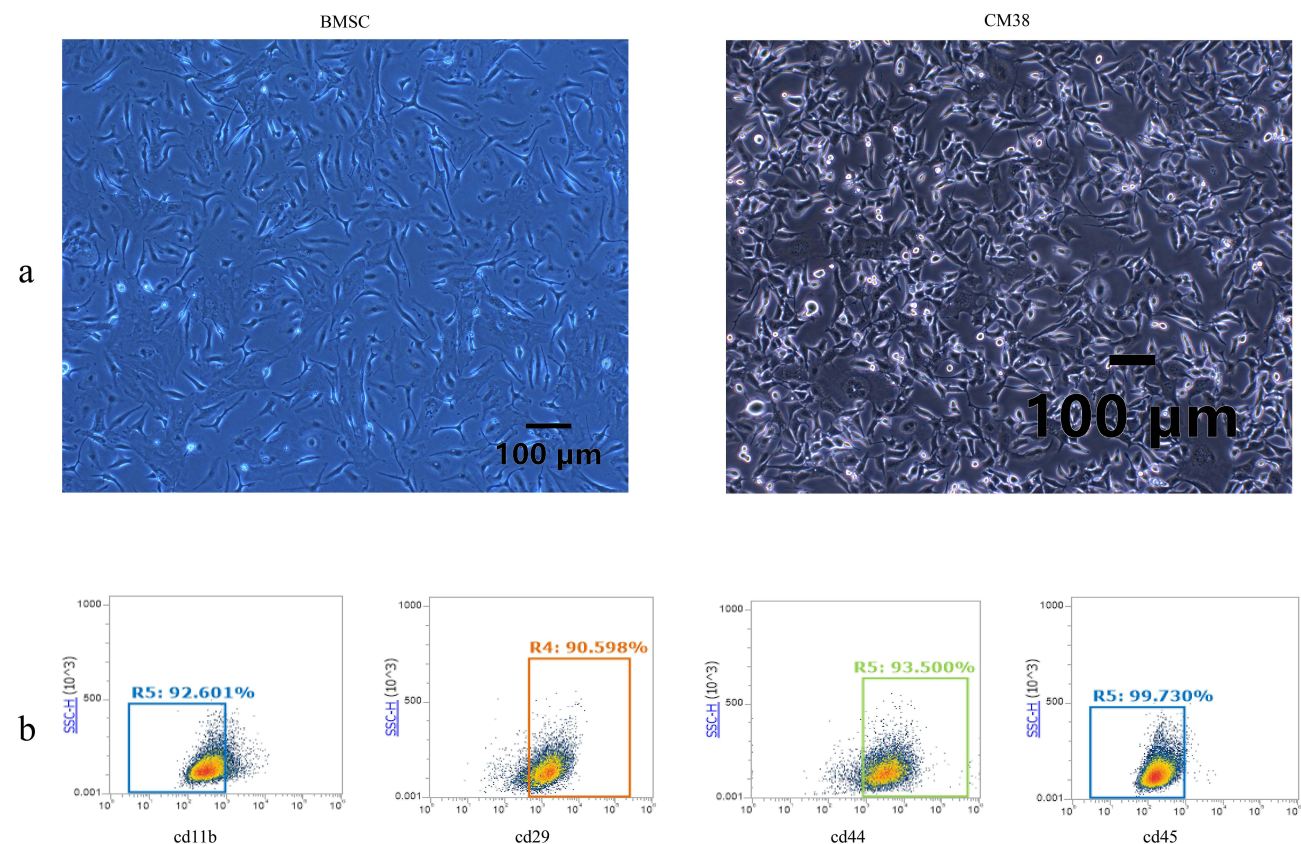
## Results

Third-passage mesenchymal stem cells (MSCs) exhibited a spindle-shaped morphology with adherent growth. Flow cytometry analysis revealed high positive expression of stem cell markers CD29 (90.6%) and CD44 (93.5%), while demonstrating negative expression of CD11b (92.6%) and CD45 (99.7%). CM38 cells displayed adherent growth characteristics with small cell size, high nuclear-to-cytoplasmic ratio, and dense cellular proliferation (Figure 2).

MRI examinations at postoperative day 7 confirmed tumor growth without visible cutaneous protrusion. One control group mouse died after the initial MRI scan due to hypothermia. All remaining mice developed tumors at the implantation site within 9 weeks. 5 tumors (2 in the control group; 3 in the intervention group) reached the maximal diameter of 15 mm–20 mm by Week 3. 28 tumors (12 controls; 16 intervention) by Week 4. 20 tumors (11 controls; 9 intervention) by Week 5. 2 tumors (controls) by Week 7. 1 tumor (control) by Week 10 (Table 1).

Additional mortality included 2 mice of control group died without cause at 2 and 3 weeks after tumor implantation, respectively, and the maximum diameter of tumor was less than 15 mm. It can be seen that the tumor growth rate in the intervention group is faster than that in the control group, which indicating tail vein injection of stem cells in the early stages of tumors can promote tumor growth.

At Week 1 post-implantation, MRI revealed no statistically significant difference in tumor volume between groups ( $P = 0.21$ ). However, upon reaching the first tumor size threshold (15mm–20 mm maximal diameter at Week 3), the MSC intervention group demonstrated significantly larger tumor volumes ( $99.8 \pm 45.9 \text{ mm}^3$ ) compared to controls ( $72.0 \pm 37.2 \text{ mm}^3$ ,  $P < 0.05$ ).



**Figure 2** (a) Bone mesenchymal stem cells (MSCs) and colon cancer cells (CM38); (b) The expression of CD11b, CD29, CD44, and CD45 on BMSCs.

**Table 1** Time of Tumor to Grow to a Diameter of 15–20 mm

Group \ Week	Control	Intervention
3	2	3
4	12	16
5	11	9
7	2	0
10	1	0

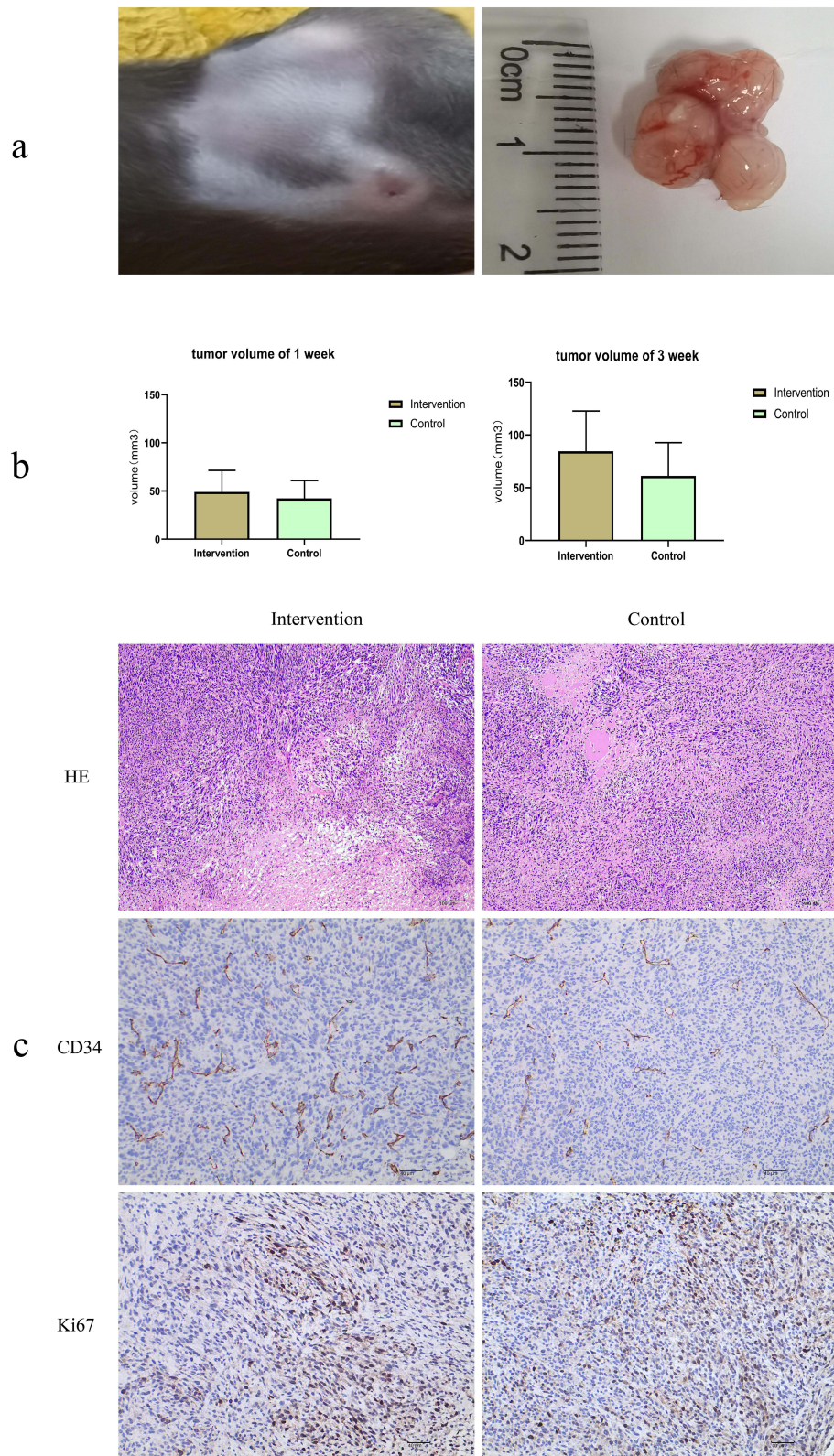
Immunohistochemical analysis showed CD34 expression rate of intervention ( $3.05\% \pm 1.16\%$ ) compared to controls ( $2.72\% \pm 0.44\%$ ,  $P < 0.05$ ), but Ki67 expression levels had no significant intergroup differences ( $19.48\% \pm 7.02\%$ ,  $26.81\% \pm 4.01\%$ ,  $P = 0.12$ ). Which indicating that MSCs promote tumor angiogenesis but have no significant promoting effect on tumor cell proliferation (Figure 3).

Radiomic analysis revealed a total of 1,162 radiomic features extracted from imaging data. Through rigorous feature selection, 17 robust predictive features were identified, including: 10 texture features, 6 first-order features, 1 shape-based feature. A total of 27 predictive models were successfully constructed, all demonstrating high discriminative performance with area under the curve (AUC)  $>0.8$  in both training and test sets (Table 2 and Figure 4).

## Discussion

This study established a predictive framework linking early-phase MR radiomic features to tumor progression in a subcutaneous colon cancer model following intravenous mesenchymal stem cell (MSC) intervention. We successfully developed 27 robust models demonstrating strong predictive performance, with area under the curve (AUC) values exceeding 0.8 in both training and test sets and optimal models achieving AUCs up to 0.88. While tumor volume remains a conventional therapeutic monitoring metric, our findings revealed no significant volumetric differences during early intervention phases. This underscores radiomics' capability to detect pre-morphological tumor alterations, particularly intratumoral heterogeneity, prior to measurable size changes. Notably, texture features dominated our selected high-correlation signatures, Dohan et al similarly demonstrated that texture analysis could predict chemotherapy response before volumetric changes, aligning with prior evidence that radiomic textures reflect tumor complexity.<sup>17,22</sup> CD34 is a factor related to the expression of new blood vessels. Kai-Hung Wang et al indicated that MSCs promote ovarian cancer cell proliferation. Wang R et al research has shown that MSC-derived VEGF via HIF-1 $\alpha$  signaling in hypoxic microenvironments.<sup>23</sup> Contrastingly, Tang RJ et al<sup>24</sup> reported tumor-suppressive MSC effects through Smad2/TGF- $\beta$ -mediated Treg differentiation in colitis-associated cancer models. This discrepancy may arise from differences between our sterile subcutaneous model and inflammation-driven carcinogenesis paradigms. The role of bone marrow mesenchymal stem cells in tumors is controlled by various growth factors, cytokines and chemokines which affect the cell proliferation, angiogenesis and metastasis. Although numerous studies have been conducted to explore the interaction between mesenchymal stem cells and cancer cells, it remains unclear how mesenchymal stem cells communicate with cancer cells and the tumor microenvironment. Further research is needed to confirm this. In our study, consistent with pro-tumorigenic MSC effects, our intervention group exhibited enhanced CD34+ neovascularization compared to controls. It is hypothesized that these significant correlated radiomics features may have a certain correlation with CD34 expression.

While preoperative MR radiomics has been validated for Ki-67 prediction,<sup>25,26</sup> we observed no significant Ki-67 expression differences between groups. This null result may reflect limited proliferative heterogeneity in our syngeneic tumor model compared to inter-tumoral variations in clinical studies. In addition, value-added often occurs after angiogenesis, so there can be a mismatch between Ki67 and CD34. This can also explain why Ki67 remains unchanged between groups while CD34 increases.

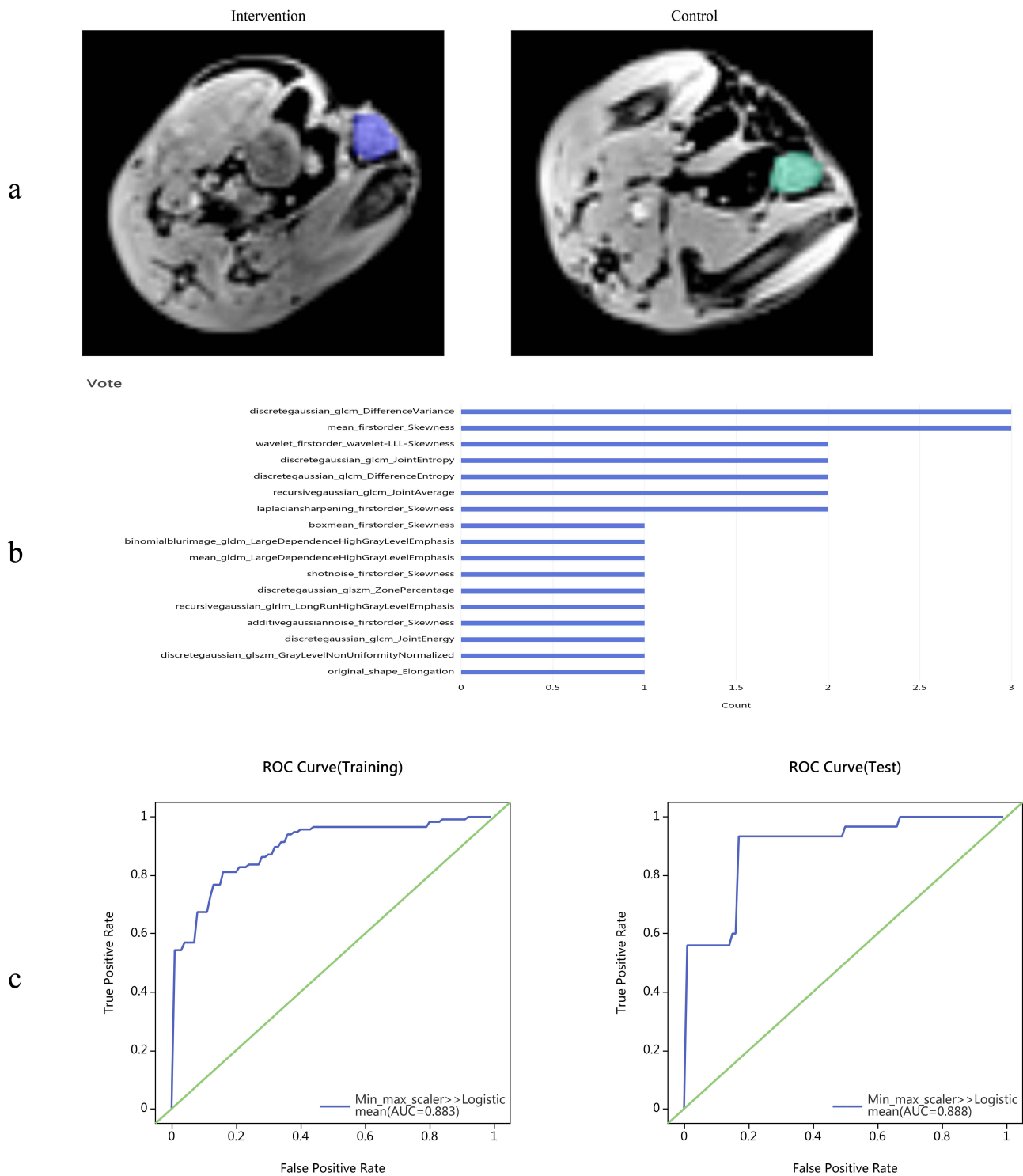


**Figure 3** (a) Subcutaneous tumor-bearing mouse and the gross morphology of the tumor; (b) Tumor volume on the 1 week and 3 week; (c) HE staining of tumor and the CD34, ki67 expression of tumor.

**Table 2** AUC of the 27 Radiomics Models

Method	Auc_Train	Auc_95% CI_Lower_Train	Auc_95% CI_Upper_Train	Auc_Test
BoxCox_transformer»QDA	0.867	0.779	0.975	0.893
Min_max_scaler»Logistic	0.883	0.803	0.984	0.888
Z_score_scaler»QDA	0.866	0.778	0.975	0.887
Min_max_scaler»SVM	0.885	0.805	0.984	0.882
YeoJohnson_transformer»QDA	0.864	0.775	0.974	0.882
Max_abs_scaler»SVM	0.871	0.783	0.979	0.876
Quantile_transformer»SVM	0.891	0.812	0.988	0.876
Max_abs_scaler»Logistic	0.874	0.789	0.98	0.871
Min_max_scaler»QDA	0.866	0.779	0.974	0.866
Quantile_transformer»QDA	0.855	0.762	0.968	0.866
Quantile_transformer»Logistic	0.89	0.81	0.988	0.865
Min_max_scaler»GaussianProcess	0.898	0.824	0.989	0.855
Max_abs_scaler»GaussianProcess	0.889	0.812	0.986	0.849
Quantile_transformer»GaussianProcess	0.914	0.846	0.996	0.849
YeoJohnson_transformer»GaussianProcess	0.912	0.843	0.998	0.849
BoxCox_transformer»Logistic	0.921	0.858	0.999	0.843
Z_score_scaler»GaussianProcess	0.908	0.84	0.994	0.838
Max_abs_scaler»QDA	0.825	0.719	0.949	0.837
YeoJohnson_transformer»Logistic	0.919	0.854	0.999	0.837
BoxCox_transformer»GaussianProcess	0.911	0.84	0.997	0.833
Z_score_scaler»Logistic	0.915	0.852	0.997	0.816
Quantile_transformer»PLSDA	0.902	0.825	0.995	0.815
BoxCox_transformer»PLSDA	0.894	0.818	0.989	0.804
Max_abs_scaler»PLSDA	0.899	0.827	0.989	0.804
Min_max_scaler»PLSDA	0.899	0.827	0.989	0.804
YeoJohnson_transformer»PLSDA	0.897	0.822	0.991	0.804
Z_score_scaler»PLSDA	0.899	0.827	0.989	0.804

Despite achieving predictive success, our study has limitations. The modest sample size ( $n = 30$ ), though ethically justified by animal use minimization principles, constrains radiomics' generalizability. To mitigate overfitting, we implemented five-fold cross-validation, enhancing model reliability despite limited data. Additional limitation of this study is lack the complexity of an orthotopic model and its exclusive identification of tumor progression-promoting effects, with no capacity to detect or predict tumor-suppressive responses. This critical gap will be systematically addressed in subsequent experimental validations to delineate dual regulatory mechanisms of stem cell intervention.



**Figure 4** (a) ROI delineation of tumor; (b) Voting results of strongly correlated features; (c) AUC of the radiomics model in training and test sets.

## Conclusion

Tail vein injection of mesenchymal stem cells in 12 hours after subcutaneous inoculation of tumor cells in the groin of mice, tumor growth was accelerated and CD34 expression in the tumor increased, indicating that mesenchymal stem cells have a promoting effect on tumor progression in the initial stage of tumor formation. In addition, the AUC of the model for predicting tumor progression using magnetic resonance imaging radiomics analysis in the early stage of tumor formation was greater than 0.8, indicating that radiomics can predict tumor progression in the early stage of tumor intervention.

## Data Sharing Statement

Data can be made available upon reasonable request to the corresponding authors.

## Acknowledgments

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## Disclosure

There was no competing interest in this study, as no paid employment, no patent application, and no author will benefit from this study.

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