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**Artificial intelligence powered radiomics model for the assessment of colorectal tumor immune microenvironment**

AI-Powered Radiomics for Colorectal Tumor **Immune-Profiling**

Shashank Kumar

## **Abstract**

Zhou *et al.*'s investigation on the creation of a non-invasive deep learning method for colorectal tumour immune microenvironment evaluation using preoperative computed tomography radiomics published in the *World Journal of Gastrointestinal Oncology* is thorough and scientific. The study analyzed preoperative computed tomography (CT) images of 315 confirmed colorectal cancer patients, using manual regions of interest to extract deep learning (DL) features. The study developed a deep learning model using CT images and histopathological images to predict immune-related indicators in colorectal cancer patients. Pathological (Tumor-stroma ratio, tumor-infiltrating lymphocytes infiltration, immunohistochemistry, tumor immune microenvironment and immune score) parameters and radiomics (CT imaging and model construction) data were combined to generate AI-powered models. Clinical benefit and goodness of fit of the models were assessed using receiver operating characteristic, area under curve and decision curve analysis. The developed DL-based radiomics prediction model for non-invasive evaluation of tumour markers demonstrated potential for personalised treatment planning and immunotherapy strategies in CRC patients. The study, involving a small group from a single medical centre, lacks inclusion/exclusion criteria and should include clinicopathological features for valuable therapeutic practice insights in CRC patients.

**Key Words:** Colorectal cancer; Machine learning model; Immune markers; Tumor microenvironment; Preoperative therapy decision; Cancer

**Core Tip:** The present hospital-based retrospective research designed an artificial intelligence- and pathological data-based predictive model to make preoperative immunotherapy decisions in CRC patients. The study includes a small number of individuals from a single medical centre. Study claims deep learning radiomics models based on tumour immune microenvironment assessment for personalised immunotherapy decisions in CRC patients. The study lacks inclusion and exclusion

criteria, particularly the exclusion of patients having other malignancies and prior treatment/immunotherapy status. The analysis should look at the clinicopathological features (age, sex, how well the tumour is differentiated, stage, lymph node status, lymphovascular invasion, and perineural invasion) of patients in both the training and validation groups. These metrics will yield valuable insights for therapeutic practice.

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## **TO THE EDITOR**

I am delighted to read the high-quality article by Zhu *et al.*[1], published in the *World Journal of Gastrointestinal Oncology*. In this study, from January 2021 to September 2023, 315 colorectal cancer (CRC) patients were randomly assigned to training (220) or validation (95) cohorts in a ratio of 7: 3. Training and validation groups have similar clinical characteristics, according to statistical analysis. This study integrates computed tomography (CT) imaging and pathology data from CRC patients using DL to construct and verify an immune microenvironment prognostic model. First, pathologists identified the tumor's highest infiltration region using a blinded approach. Sections were stained, and the Tumor-stroma ratio (TSR) was calculated and classified as high TSR (> 50%) and low TSR ( $\leq$  50%). Next, tumor-infiltrating lymphocyte infiltrations (TILs) were graded (0-3) based on tumour infiltration in pathological sections: No lymphocyte reaction, dispersed lymphocytes, moderate lymphocyte reactivity, and considerable infiltration disturbing tumour cell integrity. Low (grade 0-1) and high (grade 2-3) TILs were assigned to the cases. Immunohistochemistry identified CD3+ and CD8+ T lymphocytes in the tissue using EnVision-stained paraffin sections. Images were used to measure immune cell count (IS) in patients, with high IS (> 2) and low IS ( $\leq$  2) being considered high and low, respectively. Elevated TSR, TILs, and IS levels, patients were assigned a score, indicating low tumor immune microenvironment (TIME) (0 or 1), while scores of 2 or 3 indicated high TIME (1-3). Radiomics work included defining CRC patients' regions of interest (ROIs) before surgery using CT scanning. Radiologists used ITK-SNAP software to delineate ROIs, and the crop tool extracted the largest ROI cross-section. PyRadiomics extracted radiomic characteristics

from ROIs without notable difference. The ImageNet dataset was used to pre-train several models (ResNet-34/50/101/152, DenseNet-121/169/201). Visualising and analysing the model using Gradient Weighted Class Activation Mapping (Grad-CAM) improved transparency and knowledge of its decision-making process. The models' prediction accuracy was examined using ROC (Receiver Operator Characteristic) curves, AUC values, calibration curves, and decision curve analysis (DCA). The DenseNet-169 and DenseNet-121 models were chosen as the expected TSR DL and TILs prediction models, respectively, based on the AUC values for the training and validation sets. Similarly, DenseNet-121 and DenseNet-169 were identified as the best models for predicting high and low IS and TIME scores, respectively. DCA curves showed that the models had positive clinical utility and robust correlations, indicating an accurate labelling prediction. The violin plot revealed important differences in probability distributions among the four models, showing that the predictive model can effectively identify and detect changes in the immune microenvironment in CT data.

CRC, the third most diagnosed cancer globally, saw 2 million new cases in 2020, with 10% of patients under 50. By 2040, 3.2 million new cases and 1.6 million deaths are predicted, with 80% occurring in high or very high Human Development Index (HDI) countries[2,3]. Metabolic syndrome, characterised by hyperglycaemia, dyslipidaemia, abdominal obesity, and hypertension, is linked to increased colorectal cancer risk (25%) and mortality, with inconsistent results[4]. Tobacco use is associated with an increased incidence of colorectal cancer, while alcohol consumption-particularly ethanol intake of 50 g or more per day-is linked to both a higher risk and greater mortality[5,6]. CRC may originate from hereditary disorders. Lynch syndrome, a genetic disorder characterised by a DNA mismatch repair deficit, results in the loss of certain genes, indicating microsatellite instability in CRC[7]. Hereditary nonpolyposis colorectal cancer (HNPCC) is another genetic illness caused by a mutation in a DNA mismatch repair system, affecting 2% to 3% of all colorectal malignancies and affecting approximately 1 in 500 people[8]. An international study identifies four consensus molecular subtypes (CMSs, 1-4) for prognostic classification of primary tumors, based on

microenvironment, metabolic signatures, genomic, epigenomic, and molecular aberrations[9]. The immunoscore, an immune-based assay, quantifies CD3 and CD8-positive T cells in the tumor microenvironment, inversely linked with the disease recurrence. However, its use in clinical settings is limited. Pathogenic risk factors for recurrence or distant metastasis in <sup>3</sup> advanced colon and rectal cancer include T4 tumors, N2 disease, inadequate lymph node dissection, invasion, tumor deposits, poorly differentiated histology, or a combination[10, 11].

Tumour transformation is complicated and compromises normal cell-tissue balance. Cancer research has shifted its emphasis to the tumour microenvironment (TME), a dynamic and diverse assemblage of immune and other cells together with extracellular matrix constituents. The TME is essential for antitumor immunity and a potential tumour immunotherapy target[12-14]. Radiomics, a new analysis tool, can extract high-throughput quantitative data from medical images to explain tumour characteristics and heterogeneity. This information aids clinical practice, tumour grade prediction, and therapy selection[15, 16]. This report assesses the utility of a radiomic imaging-based model combined with the tumor immune microenvironment feature assessment for the pre-operative clinical personalised immunotherapy decisions in CRC patients. They reported that CT-based DL radiomics from preoperative TIME allow personalised immunotherapy methods in CRC management. Although their data is intriguing, I have some issues with the paper. The study lacks inclusion and exclusion criteria. I suggest some of the important inclusion criteria, such as histologically confirmed CRC samples, preoperative CT scan availability, and TIME data availability, especially with immunohistochemistry profiling of CD3+ and CD8+ T lymphocytes. The study should exclude participants with prior neoadjuvant therapy or those who are older (or the specific age group should be mentioned), as per the study design. Aging leads to immunosenescence, affecting tumor immune microenvironment composition. Including older patients may introduce age-related immune changes, potentially affecting tumor-specific responses[17]. Similarly, exclusion criteria may include exclusion of poor-quality or incomplete CT imaging, patients with a history of other malignancies within

the past five years, incomplete clinical or pathological data, prior treatment affecting the immune profile, *etc.* Generally, this five-year timeframe in the exclusion criteria is used due to key considerations such as risk of recurrence, treatment interference, potential for confounding comorbidities, and five-year standard window in many oncology clinical trial protocols. Cancers have a higher risk of recurrence within the first five years after treatment, so including patients with a recent history of other malignancies could confound the results of a study. Patients with residual effects from previous treatments could interact with the study intervention, making it difficult to assess its impact. The five-year window is a standard in oncology clinical trial protocols to minimize confounding factors[18].

Immunotherapy affects the tumor's immune milieu; thereby, enrolling those individuals might bias TIME results, especially when studying tumour immune context or baseline prognostic markers. The study makes no mention of the immunotherapy status of the enrolled patients. CD8+ T-cells are key cytotoxic effectors, directly killing tumor cells, while CD4+ T-cells support and regulate immune responses, with high infiltration indicating better prognosis and immune checkpoint response. Focusing solely on CD8+ and CD4+ T-cells is limited, as regulatory T-cells suppress anti-tumor immune responses, potentially causing negative prognoses in some cancers but complex in CRC[19]. Furthermore, tumor-associated macrophages (TAMs), with M1-type being pro-inflammatory and tumor-suppressing and M2-type being immunosuppressive and tumor-promoting, often dominate colorectal cancer and are linked to worse outcomes[20]. Moreover, recent research reveals that B cells and tertiary lymphoid structures (TLS) boost anti-tumor immunity, especially in CRC tumours with high microsatellite instability (MSI-high) [21]. In addition, neutrophils and SOX2 proteins are some other examples which have been used as tumor infiltration markers for imaging-based studies in tumor patients[22]. Even though CD4+ and CD8+ T-cells are important indicators, studying the TIME in CRC through innate immune cells and suppressive groups gives better predictions for outcomes and treatment responses.

Clinicopathological features of training and validation cohort patients are missing from the investigation. The author should include baseline features such as age, sex, tumor differentiation (high, middle, and low), stage, lymph node status, lymphovascular and perineural invasion, *etc.* These baseline features help in the correlation of study outcome data with a broader perception. [Cui et al.\[23\]](#) used preoperative CT scans to forecast TSR status and overall survival (OS) in a large group of CRC patients from multiple centres by using a multitask DL model. They also tested the approach for predicting the benefit of adjuvant chemotherapy. The study included 2268 individuals, 81% of whom had stage II or III CRC. The multitask deep learning (MDL) model developed by [Cui et al.\[23\]](#) effectively predicted overall and disease-free survival in CRC patients, with high MDL scores benefiting from adjuvant chemotherapy for stage II and III disease, despite clinicopathological variables. Thus, the study indicates the model is more authentic for stage II or III CRC patients, based on which the prospective study may be designed. [The prospective study needs to be tested on a new set of patients to ensure its generalizability. The study could evaluate the model's impact on real-world clinical decision-making, compare it to standard risk assessment tools, and include patients from diverse backgrounds. The study could also collect detailed clinical data to identify areas for improvement and uncover new biomarkers related to survival in CRC. Positive results would be more convincing to clinicians and regulatory bodies.](#) In a different study, [Li et al.\[24\]](#) developed deep learning-based prognosis (recurrence risk) using preoperative CT images, and the findings were correlated with several clinicopathological parameters. Integrated nomogram construction in association with clinicopathological features and DL CT image features with paired gene expression profiles were altogether able to predict prognosis in CRC patients. The study incorporated baseline clinicopathological features such as age, sex, tumor stage, lymph node and metastasis status, and differentiation grade [\[24\]](#).

## CONCLUSION

This hospital-based retrospective study possesses limitations due to the limited cohort of participants and **lack of multi-centre data**. The trial lacks defined inclusion and exclusion criteria, which can alter the tumor immune microenvironment and thereby the inappropriate pre-operative immunotherapy clinical decisions in CRC patients. **Furthermore**, lack of baseline clinicopathological features of the study patients limits the applicability of the proposed model in CRC patients. A prospective study design is necessary, incorporating a larger sample size from multiple centres, detailed tumour histopathological data, and expanded inclusion and exclusion criteria to achieve more reliable and generalised outcomes for preoperative immunotherapeutic clinical decisions in CRC patients.

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SIMILARITY INDEX

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