Machine Learning-based Prediction of Metastasis-Level Response to Combined SBRT and Immunotherapy

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ABSTRACT

Although immune checkpoint blockade (ICB) benefits only a subset of patients, combining ICB with stereotactic body radiation therapy (SBRT) may enhance therapeutic response. Building on a validated CT-based radiomics score (RS) that predicts patient-level response to SBRT plus pembrolizumab (SBRT+P), this retrospective study developed a machine-learning (ML)-based approach to predict metastasis-level response by identifying lesions susceptible to SBRT-induced T-cell infiltration, with the goal of enabling more informed treatment decisions for patients with multiple metastases. This retrospective study included 68 patients with 140 metastases, who received site-specific SBRT followed by pembrolizumab within 7 days. Metastatic response was assessed at first follow-up (3 months) and defined as a ≥30% reduction in lesion diameter. For each metastasis, 85 features were extracted, including 41 intratumoral radiomics features, 41 peritumoral radiomic features, and 3 lesion-location indicators. An ML-based prediction framework incorporating backward feature selection and shuffle–split validation was developed to predict metastasis-level response. Kernel SHAP was employed to quantify the contribution of selected features to model predictions, enabling interpretation of feature–response relationships while accounting for nonlinear feature interactions. Model performance was compared with a radiomics score–based logistic regression model (RS-Logistic). Forty-five of 140 metastases (32%) responded to SBRT+P. The ML model outperformed the RS-Logistic (AUC = 0.77 vs. 0.68). Five features were selected, including intratumoral and peritumoral intensity and textural features, and a lesion-location indicator distinguishing osseous from soft-tissue lesions. Soft-tissue metastases with dense and homogeneous cores, sharp local intensity gradients, and irregular peritumoral boundaries were more likely to respond, whereas osseous metastases were associated with treatment resistance. The proposed ML model integrates radiomic features of metastases and their peritumoral microenvironment with lesion location to predict lesion-level response to combined SBRT-immunotherapy. Further studies are warranted to validate the predictive value of these biomarkers in larger, external cohorts.

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INTRODUCTION

Immune checkpoint blockade (ICB) is a pivotal cancer therapy, yet most patients exhibit limited response. Combining ICB with stereotactic body radiation therapy (SBRT) may improve the local response to radiation and the systemic response to immunotherapy.

Previously, the radiomics score (RS), a CT-based radiomics signature of tumor immune infiltration, was validated as a predictive biomarker to identify patients with metastases responsive to SBRT plus pembrolizumab (SBRT+P).

Moving beyond this single-score method for patient-level response assessment, the present study explored machine learning (ML) models to predict metastasis-level response to SBRT+P.

Via a retrospective study, we aimed to identify metastases prone to SBRT-induced T-cell infiltration, enabling improved lesion-level stratification of treatment benefit. This approach may support more informed decision-making for multi-metastatic treatment planning and follow-up strategies.

METHODS AND MATERIALS

Patient & Treatment: 68 patients including a total of 140 metastases from a phase I trial evaluating SBRT followed by pembrolizumab for metastatic solid tumors. Site-specific SBRT (30–50 Gy in 3–5 fractions) was delivered every other day, with pembrolizumab (200 mg IV every 3 weeks) started within 7 days after SBRT.

Response Evaluation: Metastasis response was assessed every 3 months using RECIST 1.1 (soft tissue) and MD Anderson criteria (bone metastases). Response at first follow-up: Soft-tissue lesions with ≥30% shrinkage and bone lesions with radiologic normalization were classified as responders; all others were classified as non-responders.

Feature Extraction: Treatment-planning CT was used to extract 85 features per metastasis, including 82 radiomic features (41 intratumoral and 41 from a 4-mm peritumoral ring, comprising histogram, shape, and texture metrics) and 3 anatomical locations indicating peripheral lung/visceral, central lung/mediastinal, or osseous/spinal sites.

ML-based Prediction Modeling: Our ML-based prediction framework is outlined in Figure 1. Four classifiers (SVM-Linear, SVM-RBF, SVM-Poly, and Random Forest) were trained along with sequential backward feature selection and 80/20 shuffle-and-split validation to predict metastasis response while reducing overfitting. For comparative analysis, we calculated the radiomics score for each metastasis. The RS was defined as a linear combination of eight variables: five radiomic features (one first-order statistic and four second-order Gray-Level Run Length Matrix metrics), two anatomical location indicators (adenopathy and head & neck), and the CT peak kVp. For comparison purposes, a logistic regression model was also fitted using the RS to predict metastatic-level response.

Feature interpretation: Kernel SHAP was used to interpret the best-performing model by quantifying each feature's contribution to the prediction and its relationship with treatment response.

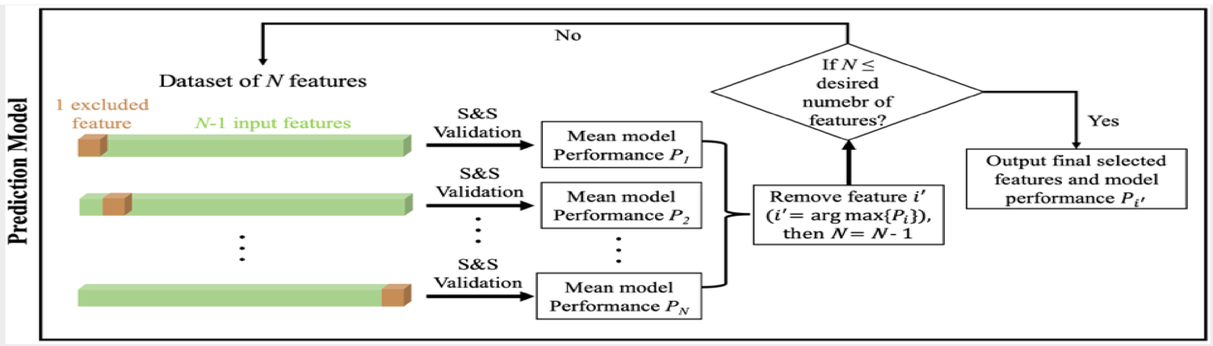

Figure 1. Framework of the ML-based prediction model.

RESULTS

Model Performance: Of 140 metastases, 45 (32%) responded to SBRT+pembrolizumab. The SVM-Poly classifier was the best-performing model, achieving AUC 0.77 and 70% accuracy using the five most discriminative features, outperforming the radiomics score model (AUC 0.68, 63% accuracy), as is shown in Figure 2.

Selected Features: The five selected features (Table 1) included intratumoral intensity (HISTO_Energy) and texture (NGLDM_Contrast, GLZLM_SZE), peritumoral heterogeneity (HISTO_Entropy_log10_ring), and the osseous/spinal location marker (loc3), capturing tumor density, texture, the surrounding microenvironment, and anatomical site

Feature Interpretation: SHAP analysis (Figure 3) showed that greater peritumoral heterogeneity (HISTO_Entropy_log10_ring), higher lesion density (HISTO_Energy), and greater intratumoral heterogeneity (NGLDM_Contrast) were associated with an increased probability of response, whereas coarser tumor texture (lower GLZLM_SZE) and osseous/spinal metastases (loc3)were associated with a lower probability of response.

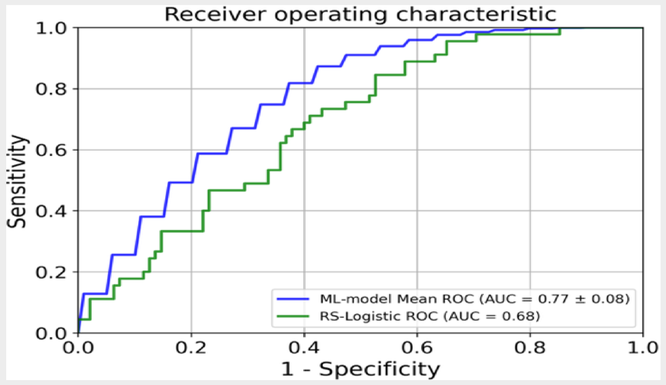

Figure 2. Performance evaluation of the SVM-poly classifier versus the RS-based logistic model.

Table 1. The five most discriminative features used in the SVM-poly.

Feature	Category	Description
HISTO_Energy	First-order (GTV)	Sum of squared voxel intensities
NGLDM_Contrast	Texture (GTV)	Neighborhood Gray-Tone Difference Matrix Contrast
GLZLM_SZE	Texture (GTV)	Gray-Level Zone Length Matrix Small Zone Emphasis
HISTO_Entropy_log10_ring	First-order (ring)	Randomness of intensity distribution
loc3	Anatomical	Osseous/Spinal/Paraspinal

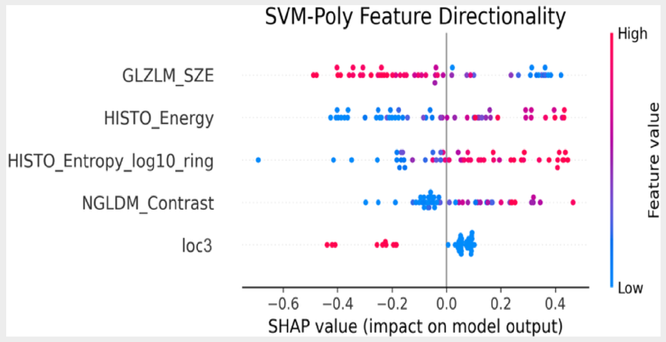

Figure 2. SHAP summary plot illustrating the impact of selected radiomic and anatomical features on model prediction.

DISCUSSION

- ML outperformed the radiomics score model (AUC 0.77 vs. 0.68).
- Both the tumor and its peritumoral microenvironment, together with lesion location, may determine the response to SBRT + pembrolizumab.
- Dense soft-tissue lesions with coherent homogeneous regions, sharp local intensity transitions, and irregular peritumoral boundaries were more likely to respond to SBRT + pembrolizumab.
- External validation in larger cohorts is needed confirm the predictive value of the selected features.

CONCLUSIONS

The proposed ML framework leverages features from the tumor, peritumoral microenvironment, and lesion location to enable lesion-level prediction and support personalized SBRT–immunotherapy planning.

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