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Multi-scale Dose-defined Lung Subregional Dosiomics for Radiation Pneumonitis Prediction in VMAT With Conventional Fractionation

Geon Oh, PhD[1]; Chanil Jeon, PhD[1]; Jaehwan Lee, MS[1]; Haenghwa Lee, PhD[1]; Sung Hun Kim, PhD[1]; Dongho Shin, PhD[1]; Dongseok Shin, PhD[1]; Jaeman Son, PhD[2]
[1]Proton Therapy Center, National Cancer Center, Goyang, Republic of Korea
[2]Department of Radiation Oncology, Seoul National University Hospital, Seoul, Republic of Korea

ABSTRACT

This study aimed to develop and evaluate a multi-scale dose-defined lung subregional dosiomics approach for predicting radiation pneumonitis in lung cancer patients treated with conventionally fractionated VMAT. This retrospective study included 118 patients treated with conventionally fractionated VMAT, split into a training cohort (n=99) and a held-out test cohort (n=19). RP grade ≥2 occurred in 33.9% patients. Dose-defined lung subregions were generated using cumulative dose thresholds and interval dose bands, along with the whole-lung ROI. From each ROI, 3D dosiomics features were extracted (1409 features/ROI) to form cumulative, interval, and hybrid feature sets. A feature selection pipeline consisting of z-score normalization, t-test screening, redundancy removal, and ℓ2,1-norm minimization with bootstrap-repeated stratified cross validation was used to select stable top-k features and train a logistic regression model. Model performance was evaluated using AUC and PR-AUC. In internal validation (10-fold cross-validation), the hybrid feature set achieved the highest performance (AUC 0.870; 95% CI: 0.807–0.937), outperforming whole-lung dosiomics (AUC 0.683; 0.629–0.729) and standard DVH metrics (V5, V10, V20, MLD; AUC 0.612; 0.573–0.658). The Hybrid model also demonstrated strong precision–recall performance (PR-AUC 0.823; 0.751-0.889), indicating improved discrimination under class imbalance. In the test cohort, the Hybrid model remained superior (AUC 0.846; PR-AUC 0.741) compared with whole-lung dosiomics (AUC 0.628; PR-AUC 0.568) and DVH metrics (AUC 0.593; PR-AUC 0.538). Conclusions: The multi-scale hybrid dosiomics approach demonstrated superior predictive performance compared to single-scale and conventional DVH approaches. By capturing spatial dose heterogeneity that global metrics miss, this approach facilitates more accurate RP risk prediction for patients treated with VMAT.

CONTACT

[name] Geon Oh
[organization] National Cancer Center
[address] 323, Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, Republic of Korea
[email] geonoh@ncc.re.kr
[phone] +82-10-4303-2362

INTRODUCTION

Lung cancer radiotherapy with volumetric modulated arc therapy (VMAT) achieves highly conformal target coverage but distributes a broad low-dose bath across normal lung, contributing to radiation pneumonitis (RP) in 20–40% of patients.

Conventional DVH metrics reduce a complex 3D dose distribution to volume-averaged summaries that discard spatial information. Dosiomics has recently emerged as a promising approach that treats the three-dimensional dose distribution as a quantitative image, capturing dose heterogeneity, gradients, and texture beyond DVH metrics, and has been shown to improve RP prediction—particularly when combined with radiomics or clinical variables [14–19]. In most studies, however, features were extracted from the whole lung as a single ROI.

Because the irradiated lung in VMAT comprises distinct dose environments—high-dose peritumoral regions, intermediate transition zones, and an extensive low-dose bath—aggregating them into a single region of interest (ROI) may obscure region-specific dose.

This study evaluated multi-level dose-defined subregional dosiomics for predicting RP, using cumulative dose-threshold ROIs and interval dose-band ROIs. Models based on each strategy, and their hybrid combination, were assessed and compared against conventional DVH metrics and whole-lung dosiomics to determine whether subregional spatial information improves predictive performance.

METHODS AND MATERIALS

A total of 118 patients treated with conventionally fractionated VMAT were retrospectively analyzed and divided into training (n=99) and held-out test (n=19) cohorts. Symptomatic radiation pneumonitis (grade ≥2) developed in 33.9% of patients.

To capture the spatial distribution of dose, the lungs were partitioned into dose-defined subregions using two complementary strategies.

Cumulative subregions were defined by successive dose thresholds, while interval subregions were defined by consecutive dose bands spanning the full dose range. A whole-lung ROI excluding the ITV was also generated. From each ROI, 1409 three-dimensional dosiomics features were extracted and organized into cumulative, interval, and hybrid feature sets.

Feature selection proceeded through a sequential pipeline. Features were first z-score normalized, then screened by t-test ($p < 0.05$), followed by redundancy removal for highly correlated pairs ($|r| > 0.9$). Finally, ℓ2,1-norm minimization combined with bootstrap-repeated stratified cross-validation identified stable top-k features. These features were used to train a logistic regression model, whose performance was assessed by AUC and PR-AUC.

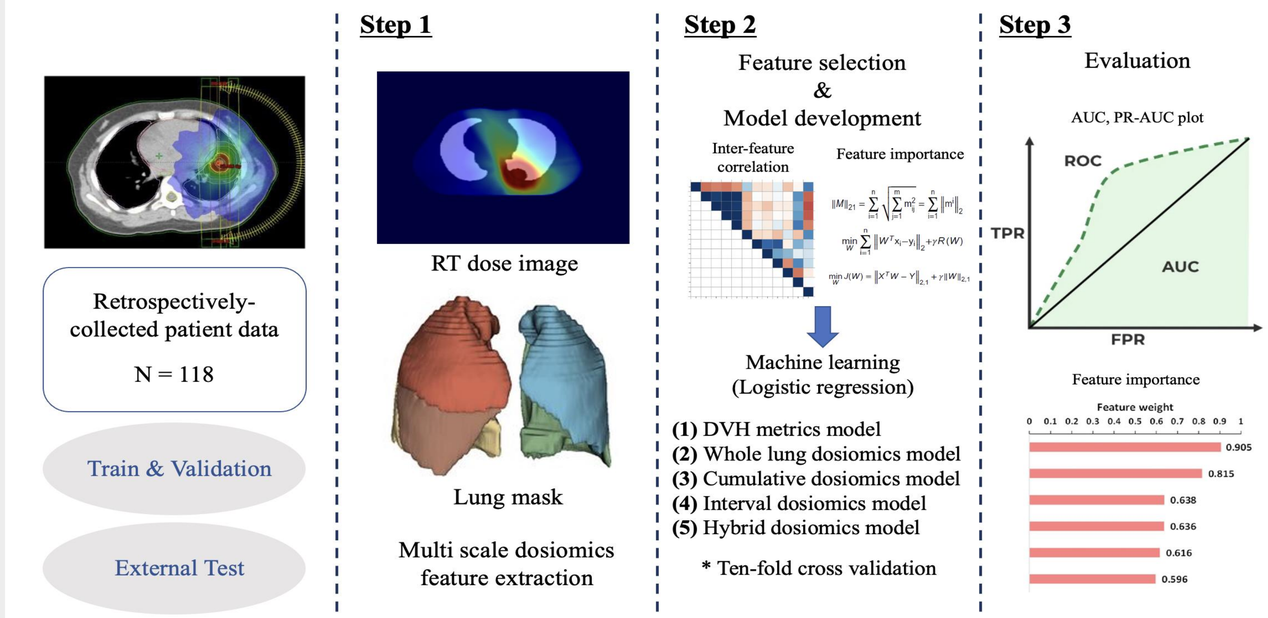
RESULTS

In the internal validation using 10-fold cross-validation, the hybrid feature set achieved the highest predictive performance, with an AUC of 0.870 (95% CI, 0.807–0.937). This performance exceeded that of whole-lung dosiomics alone (AUC, 0.683; 95% CI, 0.629–0.729) and conventional DVH-based metrics, including V5, V10, V20, and MLD (AUC, 0.612; 95% CI, 0.573–0.658).

Table 1. Predictive performance (AUC and PR-AUC with 95% CI) of the feature set models for internal validation and the the held-out test cohort

Features	AUC (95% CI)	PR-AUC (95% CI)
Internal validation		
DVIs	0.612 (0.573-0.658)	0.564 (0.511-0.616)
Whole lung features	0.683 (0.629-0.729)	0.631 (0.593-0.673)
Cumulative fea	0.769 (0.716-0.829)	0.674 (0.623-0.719)
Interval features	0.831 (0.772-0.894)	0.761 (0.684-0.839)
Hybrid Features	**0.870 (0.807-0.937)**	**0.823 (0.751-0.889)**
External test set		
DVIs	0.593	0.538
Whole lung features	0.628	0.598
Cumulative features	0.749	0.626
Interval features	0.801	0.696
Hybrid Features	**0.846**	**0.741**

Figure 1. Overall flowchart of this study



The hybrid model also demonstrated strong precision–recall performance, yielding a PR-AUC of 0.823 (95% CI, 0.751–0.889), indicating robust discriminatory ability even in the presence of class imbalance.

Consistent performance was observed in the held-out test cohort, where the hybrid model maintained the best predictive accuracy (AUC, 0.846; PR-AUC, 0.741). In comparison, whole-lung dosiomics (AUC, 0.628; PR-AUC, 0.568) and conventional DVH metrics (AUC, 0.593; PR-AUC, 0.538) showed comparatively limited predictive performance.

Feature importance analysis revealed that interval-based dosiomic features constituted the majority of the top-ranked predictors, accounting for 73.3% of the Top-30 features. Cumulative dose features also contributed substantially 26.7% and appeared repeatedly among the highest-ranked variables, including V0, V5, V20 and V35. Notably, the most informative interval dose bands were concentrated around 10–20 Gy and 35–40 Gy. Wavelet-derived texture features represented 66.7% of the Top-30 features, suggesting that multi-resolution texture patterns of dose distribution may provide important predictive information for radiation pneumonitis risk.

Figure 2. ROC curves of the five feature sets in the internal validation (left) and test (right) sets.

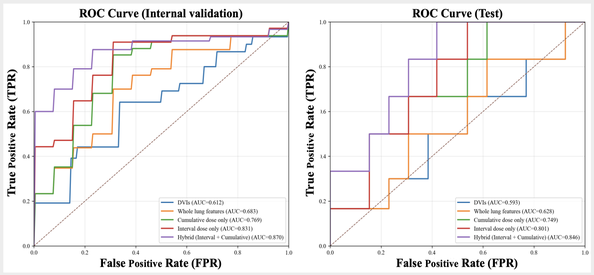
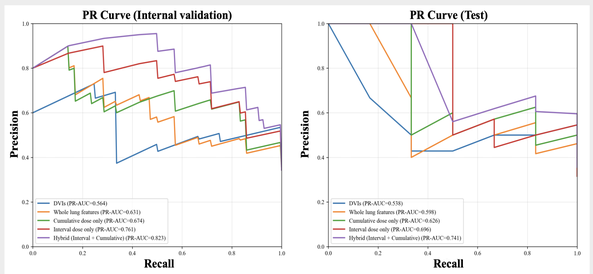


Figure 3. PR curves of the five feature sets in the internal validation (left) and test (right) sets.



CONCLUSIONS

The multi-scale hybrid dosiomics model showed higher discriminatory performance than whole-lung dosiomics and conventional DVH-based models in both internal validation and a held-out test cohort. These findings suggest that dose-defined subregional spatial heterogeneity may provide complementary information for RP risk stratification in VMAT-treated patients.

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