



Enhanced ISUP grade prediction in prostate cancer using multi-center radiomics data

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Abstract

Background To explore the predictive value of radiomics features extracted from anatomical ROIs in differentiating the International Society of Urological Pathology (ISUP) grading in prostate cancer patients.

Methods This study included 1,500 prostate cancer patients from a multi-center study. The peripheral zone (PZ) and central gland (CG, transition zone + central zone) of the prostate were segmented using deep learning algorithms and were defined as the regions of interest (ROI) in this study. A total of 12,918 image-based features were extracted from T2-weighted imaging (T2WI), apparent diffusion coefficient (ADC), and diffusion-weighted imaging (DWI) images of these two ROIs. Synthetic minority over-sampling technique (SMOTE) algorithm was used to address the class imbalance problem. Feature selection was performed using Pearson correlation analysis and random forest regression. A prediction model was built using the random forest classification algorithm. Kruskal-Wallis H test, ANOVA, and Chi-Square Test were used for statistical analysis.

Results A total of 20 ISUP grading-related features were selected, including 10 from the PZ ROI and 10 from the CG ROI. On the test set, the combined PZ + CG radiomics model exhibited better predictive performance, with an AUC of 0.928 (95% CI: 0.872, 0.966), compared to the PZ model alone (AUC: 0.838; 95% CI: 0.722, 0.920) and the CG model alone (AUC: 0.904; 95% CI: 0.851, 0.945).

Conclusion This study demonstrates that radiomic features extracted based on anatomical sub-region of the prostate can contribute to enhanced ISUP grade prediction. The combination of PZ + GG can provide more comprehensive information with improved accuracy. Further validation of this strategy in the future will enhance its prospects for improving decision-making in clinical settings.

Keywords Prostate cancer · ISUP grade · Radiomics · Machine learning · Bi-parametric MRI · Random forest model

Introduction

Prostate cancer (PCa) is the most common malignant tumor in men, and its incidence rate is leading among male cancers [1]. It is predicted that by 2024, there will be 299,010 new diagnoses of PCa in the United States, and it is expected that 35,250 people will die from the disease [2]. The Gleason score (GS), a pathology standard for evaluating PCa aggressiveness, fails to differentiate between Gleason 3+4=7 and 4+3=7, a significant flaw that impacts patient care and has spurred efforts to improve the scoring system [3, 4]. In response to this need, the International Society of Urological Pathology (ISUP) introduced a new grading and grouping system for prognostic differences in PCa, updating the traditional GS scoring system. ISUP classifies PCa into five grades, with ISUP 1 (GS ≤ 3+3) being considered the lowest risk, while ISUP 5 (GS 9–10) is considered the highest risk

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[5]. The ISUP grading provides a more precise assessment of cancer risk for patients, so an accurate identification of the ISUP grading of PCa is critical for patient prognosis, risk stratification, and the development of individualized treatment plans. Misclassification of ISUP grading in PCa can lead to inappropriate treatment decisions, such as placing a patient with a higher-grade tumor on active surveillance when they may require definitive therapy, potentially resulting in disease progression and worse outcomes.

Magnetic resonance imaging (MRI) is an important imaging tool with significant clinical implications for the diagnosis and management of PCa. Multi-parametric MRI has high sensitivity and specificity for the detection of significant cancer using three imaging sequences, typically T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCE) [6]. However, while multiparametric MRI requires the use of contrast agents and longer scan times, dual-parametric MRI (including T2WI and diffusion-weighted imaging) has the advantage of avoiding needles, avoiding injection of gadolinium enhancers, shorter scan times, and a lower price point, making it an increasingly important method of evaluation for staging and new diagnoses of PCa [7, 8]. The apparent diffusion coefficient (ADC) value is correlated with the histological grade of various malignant tumors. The DWI sequence and ADC map are considered to be the main tools for detecting and characterizing lesions through analysis [9–12]. However, the PCa risk scoring systems commonly used in imaging, such as PI-RADS [8], only assess the risk of PCa for clinical practice. It has also been found that patients with higher PI-RADS categories (4 or 5) have a greater risk of having clinically significant PCa [13, 14], but the direct correlation between PCa imaging and PCa pathologic grading to indicate severity and prognosis is underexplored.

Radiomics is an emerging field of research that explores the content related to diseases mainly by extracting a large amount of quantitative information from medical images, which can be used for various clinical applications such as disease diagnosis, prognosis assessment, and treatment response monitoring, and guide individualized treatment plans [15–18]. Some researchers [19–22] have explored small data sets and studied the application of radiomics analysis based on [68Ga]Ga-PSMA-11 PET, [18 F] PSMA-1007 PET/CT and [68Ga] PSMA PET/CT in the prediction of International Society of Urological Pathology (ISUP) grading of PCa. Other efforts try to screen patients for clinically significant PCa using the mpMRI and radiomics [23–26]. Although these studies have shown encouraging results, the conclusions drawn may not be universally applicable when the dataset is expanded due to insufficient sample size (less than 500 cases in each), and the models have weak generalization capabilities.

This study aims to use a large-scale multi-center dataset to explore the potential value of radiomics features extracted based on anatomical ROIs for continuous ISUP grading of PCa, thereby achieving a more accurate image-pathology correlation.

Methods

Patients

We reviewed the PI-CAI: Public Training and Development Dataset [27], which comprises cases from more than 1,500 instances, sourced from multiple centers (Radboud University Medical Center, University Medical Center Groningen, Ziekenhuis Groep Twente). Each patient in the PI-CAI dataset includes three imaging sequences: axial T2WI, axial DWI, and axial ADC images. All patients may include sagittal and coronal T2WI sequences, and none include dynamic contrast enhancement (DCE) sequences. The sequences are aligned using RAS coordinates [28], and most of the images are aligned well after visual inspection. Manual registration is performed for a small number of images for which the alignment is poor.

Segmentation mask

The segmentation labels of the peripheral zone (PZ) and central gland (CG, comprises the transition zone and the central zone) of the prostate were automatically performed using semi-supervised deep learning with T2WI modality [27]. Manual verification by one radiology expert was performed to ensure the quality of the anatomical mask, and did not find any obvious segmentation errors. The case examples of T2WI, ADC, and DWI images with ISUP=0–5 and the mask on T2WI at PZ/CG are showed in Fig. 1. Since we used a publicly available dataset, no institutional review board or Health Insurance Portability and Accountability Act approval was required for this study.

Feature extraction

The study design of this research is showed in Fig. 2. For the 2 ROIs and 3 sequences, Pyradiomics (<https://github.com/AIM-Harvard/pyradiomics>) [29] was used to extract shape, first order, texture, wavelet, exponential, gradient, lbp2d, lbp3d, logarithm, square, square root and log features respectively, i.e., a total of 12,918 features were extracted for each patient. During the feature extraction process, set binWidth to 25, the resampling pixel spacing to $1 \times 1 \times 1$, the resampling method to sitkBSpline, and the pad distance to 10.

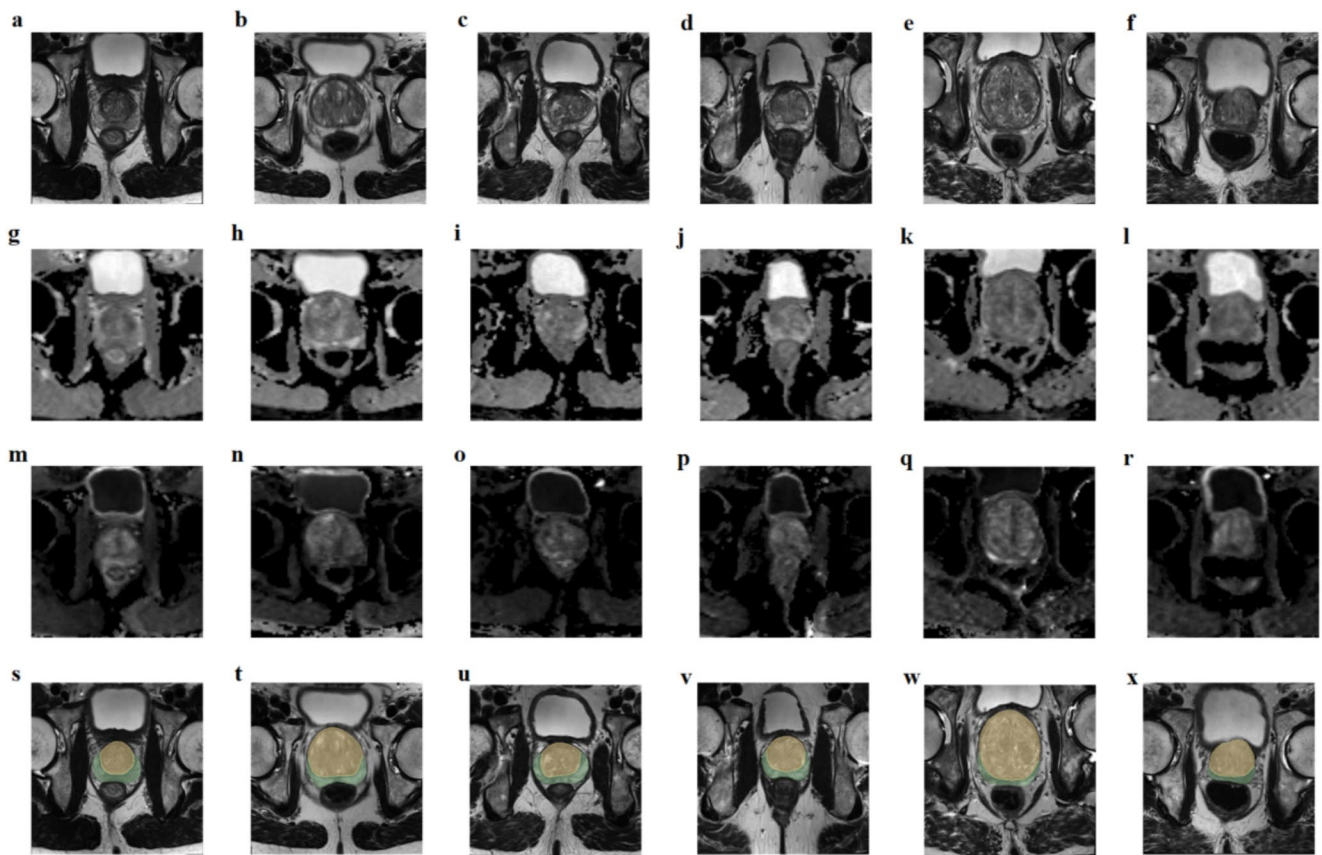


Fig. 1 Examples T2WI, ADC and DWI images and masks on T2WI in PZ/CG: ISUP 0 of T2WI (a), ISUP 1 of T2WI (b), ISUP 2 of T2WI (c), ISUP 3 of T2WI (d), ISUP 4 of T2WI (e), ISUP 5 of T2WI (f), ISUP 0 of ADC (g), ISUP 1 of ADC (h), ISUP 2 of ADC (i), ISUP 3 of ADC

(j), ISUP 4 of ADC (k), ISUP 5 of ADC (l), ISUP 0 of DWI (m), ISUP 1 of DWI (n), ISUP 2 of DWI (o), ISUP 3 of DWI (p), ISUP 4 of DWI (q), ISUP 5 of DWI (r), segmentation on T2WI of ISUP 0 (s), ISUP 1 (t), ISUP 2 (u), ISUP 3 (v), ISUP 4 (w), and ISUP 5 (x)

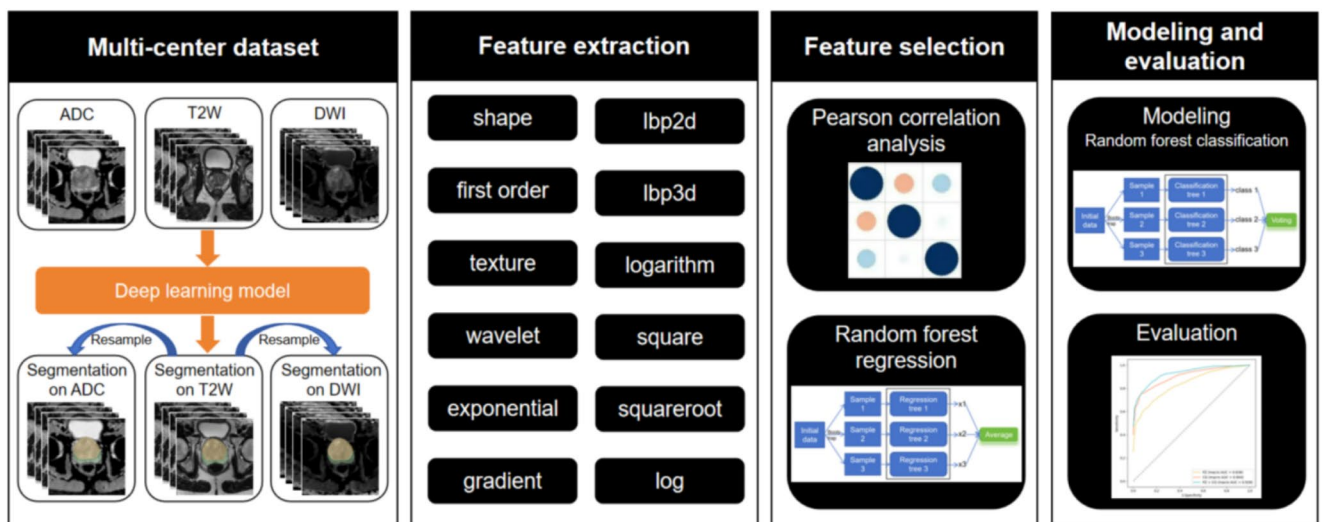


Fig. 2 The study design of our research. It includes four steps: multi-center dataset, feature extraction, feature screening and modeling and evaluation

Dataset division and data enhancement

Random sampling was employed to allocate 15% of the data for the test set, with the remainder reserved for training. Baseline characteristics of the 1500 patients used in this study are summarized in Table 1. The data set is severely class-imbalanced between different ISUP grading, so data enhancement was performed in the training set using the SMOTE algorithm [30], while the test set retained its original distribution to ensure evaluation reliability. Since the SMOTE algorithm synthesizes new minority samples in the feature space to balance the dataset, thereby increasing the number of minority samples, and then improving the model's prediction ability for the minority class, the SMOTE algorithm is also suitable for only smaller or less resourced dataset, i.e., the dataset size does not affect the reproducibility of the results.

Unstable feature exclusion

Due to differences in experimental conditions, operating procedures, sample sources, data processing methods, and other factors between research centers, some features extracted by raw imaging may be unstable. To further eliminate the impact of this factor on the experimental results, we used the intraclass correlation coefficient (ICC) [31] to eliminate features that are unstable between multiple centers, and only retained features with an $ICC \geq 0.75$. Finally, 426 unstable features were eliminated, and 12,492 stable features were obtained.

Feature selection

Pearson correlation analysis with a threshold of 0.95 was used for feature pre-screening, i.e., highly correlated features were screened out to avoid group effects. When features are highly correlated, the model may over-select one

feature while ignoring other related features. This is called the “group effect”. Since least absolute shrinkage and selection operator (LASSO) regression [32] is sensitive to outliers and cannot handle nonlinear relationships, this study uses Random forest regression with a max depth of 10 for feature selection. Finally, based on the importance of the features, 10 features were selected separately for PZ and CG modeling in the next step. For the combined PZ+CG model, a total of 20 features were used, incorporating the 10 selected features from PZ model and the 10 selected features from CG model. The feature selection process was performed only on the training set.

Model construction and evaluation

Three radiomics models were built based on different anatomical ROIs, namely the PZ model, CG model, and PZ+CG model. All models were built using a random forest classifier, and the optimal hyperparameters were determined using grid search. Model evaluation used multiple indicators such as AUC-ROC and AUC-PR curves, AUC and AUPRC values, accuracy, recall, precision, and kappa coefficient.

Statistical analysis

The Python 3.7.9 (<http://www.python.org>) software was used to perform statistical analysis of the clinical characteristics. Since ANOVA compares the differences between multiple groups in one or more dependent variables, ANOVA was used for the age variable between different groups [33]; for variables such as prostate-specific antigen level, prostate-specific antigen density, and prostate volume, since they are non-normally distributed continuous variables, the Kruskal-Wallis H test [34] was used to compare the differences between groups; for variables as the center, since the central data are unordered and independent, the Chi-Square

Table 1 Characteristics of the ISUP=0, ISUP=1, ISUP=2, ISUP=3, ISUP=4 and ISUP=5 cohort. the classes are extremely imbalanced

Characteristics	0(n=847)	1(n=228)	2(n=234)	3(n=99)	4(n=40)	5(n=52)	P-value
Age (y)	64.115±7.172	67.136±6.476	67.491±6.780	68.303±6.119	67.100±8.406	68.115±7.633	0.000 ^a
PSA (ng/mL ²)	7.900(5.357–12.000)	7.800(5.582–11.550)	9.300(6.200–13.000)	12.000(7.375–19.000)	16.000(8.950–26.800)	14.500(8.075–28.975)	0.000 ^b
Prostate volume (mL)	64.570(45.950–91.000)	49.000(35.000–68.000)	45.000(33.000–62.000)	49.000(36.250–62.750)	51.000(35.000–63.350)	54.500(38.750–68.868)	0.000 ^b
PSAd (ng/mL ²)	0.110(0.080–0.170)	0.150(0.110–0.223)	0.200(0.130–0.305)	0.230(0.155–0.400)	0.345(0.180–0.492)	0.365(0.207–0.490)	0.000 ^b
center							0.000 ^c
PCNN	161 (19.0%)	80 (35.1%)	74 (31.6%)	22 (22.2%)	7 (17.5%)	6 (11.5%)	
RUMC	475 (56.1%)	89 (39.0%)	121 (51.7%)	58 (58.6%)	27 (67.5%)	30 (57.7%)	
ZGT	211 (24.9%)	59 (25.9%)	39 (16.7%)	19 (19.2%)	6 (15.0%)	16 (30.8%)	

Notes: The results of the ANOVA analysis are displayed as mean±standard deviation; the results of the Kruskal-Wallis H test are displayed as median (P25–P75); the results of the Chi-Square Test are displayed as number (proportion). PSA: Prostate-specific antigen level; PSAd: Prostate-specific antigen density. ^a: ANOVA; ^b: Kruskal-Wallis H test; ^c: Chi-Square Test

Test was used. A P value of less than 0.05 is used as the criterion for judging whether the statistical result is significant.

Results

Baseline information

Baseline characteristics of the 1500 patients used in this study are summarized in Table 1. According to the ISUP score, there are six different statistical groups: ISUP=0, ISUP=1, ISUP=2, ISUP=3, ISUP=4, and ISUP=5. We found with increasing age, clinical variables such as prostate-specific antigen level, prostate-specific antigen density, and prostate volume all show an increasing trend.

Characteristics selected by different anatomical ROI models

The 10 important features selected by the PZ model and the CG model using the random forest regressor and the feature importance histogram are showed in Fig. 3 (a) and (b), respectively.

In the PZ model, 3 features are derived from T2WI, and 7 features are obtained from DWI, as illustrated in Fig. 3 (a). Wavelet GLcmImc1 features in T2WI have the largest weight, reflecting the heterogeneity and spatial dependence within the tumor, while high-grade prostate cancer (ISUP 3–5) generally exhibits higher heterogeneity and aggressiveness. The LBP3D and GLCM features (e.g., GlcmMCC and GlcmImc2) in the DWI sequence further capture the three-dimensional spatial heterogeneity and structural complexity of the tumor. These features play an important role in distinguishing between high-grade and low-grade tumors. Exponential transformed GLCM features (e.g., Glcmldmn and Glcmldn) may highlight the dependence and non-uniform changes in the microstructure of tumors in DWI sequences, further assisting ISUP grading. In addition, the Wavelet Large AreaHighGrayLevelEmphasis and LoG LargeDependenceHighGrayLevelEmphasis features of T2WI reflect the large-area distribution and spatial dependence of high gray value regions, respectively, and may be related to necrosis or hemorrhagic areas of high-grade tumors. The Exponential Clustershade and Busyness features of DWI capture the local contrast and texture complexity of the tumor.

In the CG model, 1 feature is derived from T2WI, 2 features are obtained from ADC maps, and 7 features are extracted from DWI, as shown in Fig. 3(b). The feature with the highest weight is the LBP3D Range feature of the T2WI sequence. The range of intensity changes through local binary patterns (LBP3D) reflects the heterogeneity of the tumor region, and high-grade tumors usually exhibit higher

heterogeneity. (ADC, LoG GlcmMCC) combines Laplacian of Gaussian filtering (LoG) and the maximum correlation coefficient of the gray co-occurrence matrix (GlcmMCC) to describe the complexity of the internal structure of the tumor. High-grade tumors usually have more complex microstructures. (DWI, Square Skewness) and (DWI, Wavelet Skewness) both analyze the asymmetry of the intensity distribution in the tumor region by means of skewness, which may be related to necrotic or hemorrhagic areas within the tumor. (DWI, Gradient Zone%) and (DWI, Gradient SmallDependenceHighGrayLevelEmphasis) are both based on gradient analysis. The former describes the sharpness of the tumor edge, while the latter reflects the local dependence of high gray level pixels. Together, they suggest that high-grade tumors may have more irregular edges and more high-signal areas. (DWI, Wavelet Clustershade) and (DWI, Wavelet Strength) both analyze the texture and signal intensity changes in the tumor area using wavelet transform. The former describes the complexity of the texture, while the latter reflects the multi-scale signal intensity distribution. High-grade tumors usually show more complex textures and significant multi-scale signal changes.

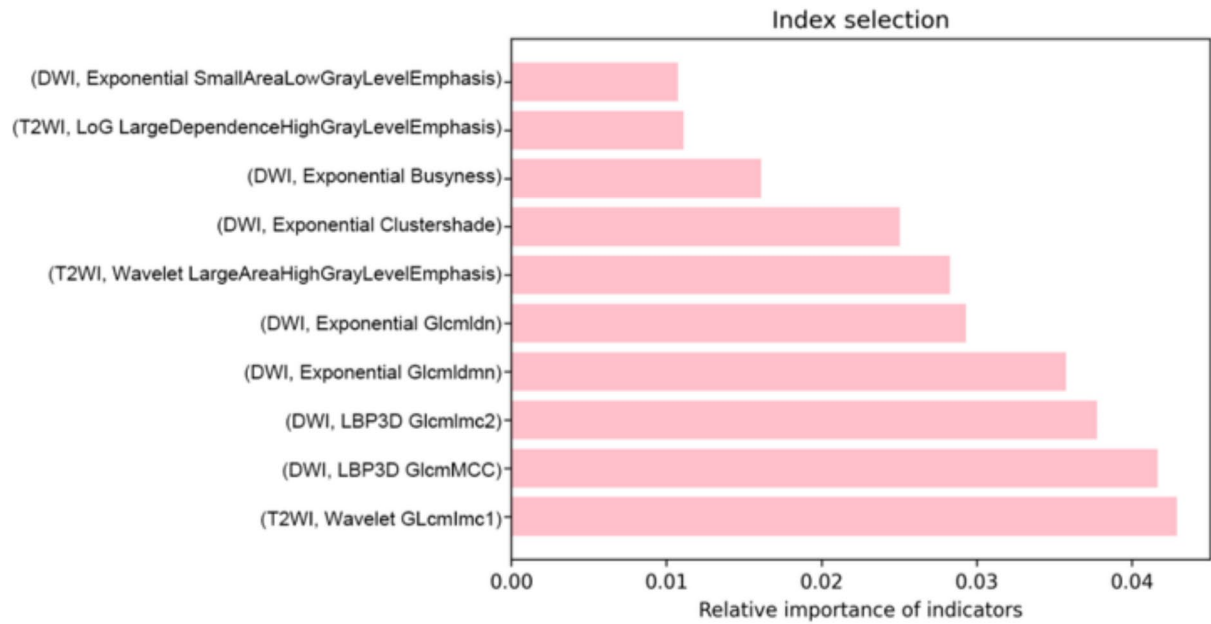
Predictive ability of different anatomical ROI models for ISUP grading tasks

The results of different anatomical ROI models for ISUP grading tasks are showed in Table 2. All models achieved relatively good AUCs on the training set. On the test set, the AUC of the PZ model was 0.838 (95%CI: 0.722, 0.920), and the AUC of the CG model was 0.904 (95%CI: 0.851, 0.945), and the PZ+CG model achieved the best performance (AUC: 0.928; 95%CI: 0.872, 0.966). The macro AUC-ROC curves and macro AUC-PR curves are shown in Fig. 4. The confusion matrix of different models are shown in Fig. 5. From Fig. 5, we find that the CG model has the best prediction effect on ISUP 1 and ISUP 5, especially ISUP 5, where the confusion matrix result reaches 1. The PZ+CG model mainly improved the prediction results of ISUP 2–4, corresponding to the intermediate and high grades of PCa. The results show that the PZ+CG model can improve the accuracy of the ISUP grading of prostate cancer to a certain extent. However, when the number of cases in a category is small, the performance will decrease slightly.

Discussion

In this paper, we used a large multi-center prostate data set to explore the predictive performance of anatomical ROI-based radiomics analysis for ISUP grading of PCa. The results showed that the combined model (PZ+CG) using

(a) 10 important features selected by the PZ model



(b) 10 important features selected by the CG model

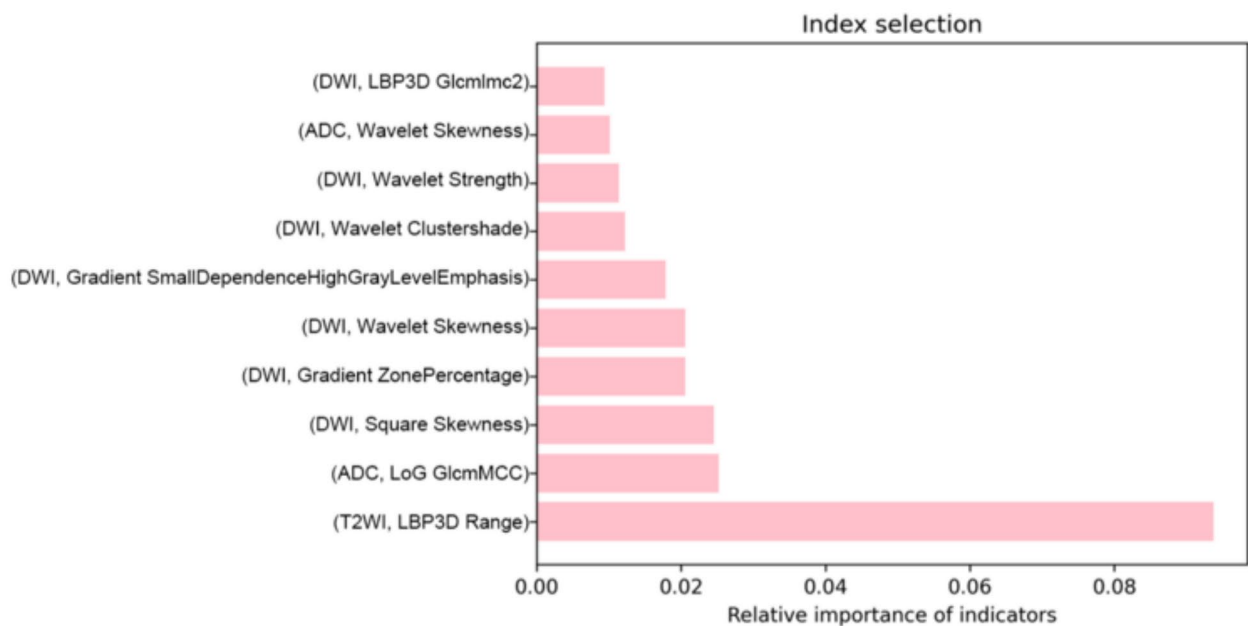


Fig. 3 A histogram of the 10 important features and the importance of the features selected by the PZ model (a), CG model (b)

the random forest classification algorithm performed better than the individual PZ and CG models on the test set.

Through biparametric MRI, radiomics, combined with a random forest algorithm, we have established a good image-pathology correlation of the PCa. This once again proves the ability of radiomics to reflect pathological grading in urological tumors. Previous studies have also confirmed that

texture features or radiomics can predict the ISUP grading of renal cell carcinoma [35–37]. In clinical settings, first, pre-determining the severity of a patient's prostate cancer is critical for deciding the best treatment plan. However, there is still some uncertainty, which may lead to the misclassification of intermediate-risk patients, which may result in excessive or unnecessary treatment. Our research results

Table 2 The results of different anatomical ROI models on the ISUP grading task. The PZ+CG model performs best on the test set

	Model	AUC (95%CI)	AUPRC (95%CI)	Accuracy	Recall	Precision	Kappa
Training set	PZ	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	0.999	0.999	0.999	0.999
	CG	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	1.000	1.000	1.000	0.999
	PZ+CG	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	1.000	1.000	1.000	1.000
Test set	PZ	0.838 (0.722, 0.920)	0.655 (0.421, 0.839)	0.581	0.656	0.518	0.403
	CG	0.904 (0.851, 0.945)	0.800 (0.607, 0.881)	0.696	0.755	0.631	0.545
	PZ+CG	0.928 (0.872, 0.966)	0.832 (0.676, 0.933)	0.722	0.767	0.681	0.587

AUC=area under the curve; AUPRC=area under the precision-recall curve; PZ=peripheral zone; CG=central gland;

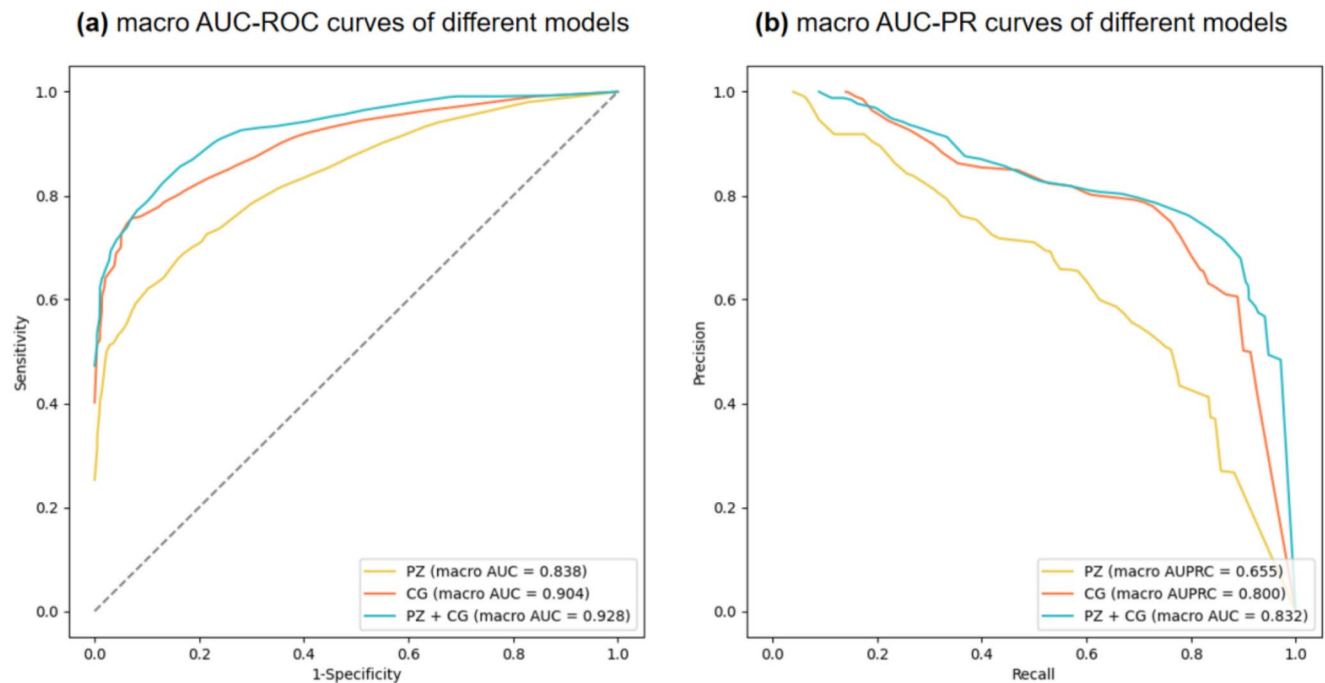


Fig. 4 (a) The macro AUC-ROC curves for different anatomical ROI models. (b) The macro AUC-PR curves for different models. Among them, the PZ+CG After model has the best AUC-ROC and AUC-PR curve performance

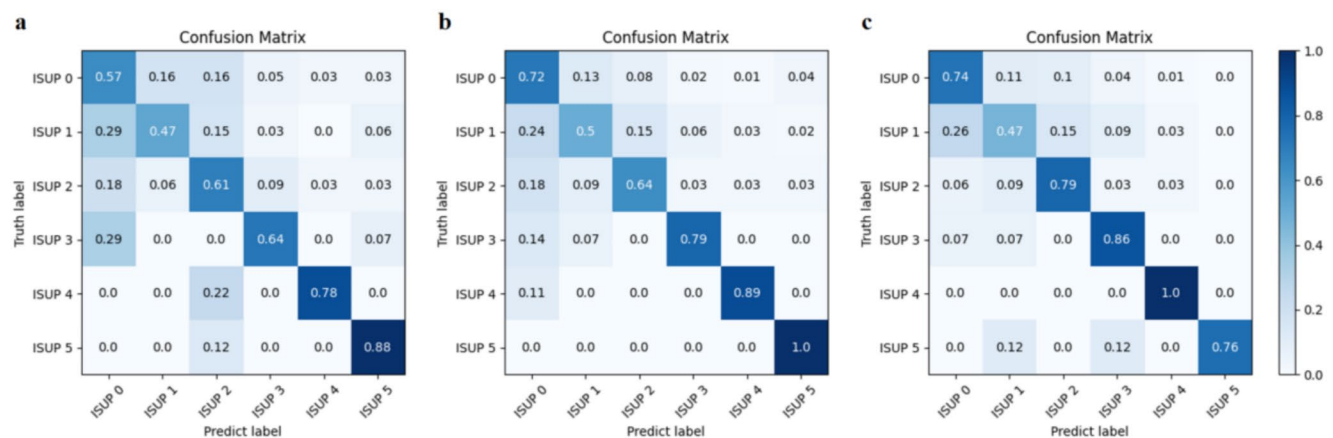


Fig. 5 Classification confusion matrix of the three anatomical ROI models. PZ model confusion matrix (a), CG model confusion matrix (b), PZ+CG combined model confusion matrix (c). The CG model

has the best performance for predicting ISUP 1 and ISUP 5, while the PZ+CG model mainly improves the prediction results for ISUP 2–4

show that radiomics feature prediction can provide a useful tool to help clinicians make more accurate diagnoses, thereby reducing unnecessary biopsy procedures and prevent misclassification of intermediate-risk patients. Second, the difference in performance between ISUP grades (e.g., grades 1,2 and 3–5) is critical to treatment decisions for patients. In particular, for patients with low-risk PCa (ISUP 1), a more conservative treatment strategy can be used due to the lower degree of malignancy, such as active surveillance [38, 39]; as for patients with intermediate-risk PCa (ISUP 2), active surveillance and brachytherapy are also two effective treatment options for favorable PCa, and partial gland ablation is a wise choice for carefully selected PCa [40]; while for patients with ISUP grade 3–5, a more aggressive treatment strategy such as surgery or radiation therapy may be required, possibly in combination with endocrine therapy or chemotherapy, due to the higher malignancy of the tumor [41, 42]. Therefore, accurate ISUP grade assessment is critical for developing an individualized treatment plan, which can help prostate cancer patients achieve better treatment outcomes and a higher quality of life.

But, previous efforts in imaging-pathological correlation in quantitative analysis of PCa [19–22], the present study achieves graded controls at fine grains instead of binary (clinically significant PCa / non-clinically significant) classification. However, all of these models require manual segmentation of the PCa region, which leads to a limited potential for clinical utility considering that these strategy requires the physician to segment the lesion layer by layer, not to mention the fact that it is more difficult to determine the boundaries of PCa compared to other tumors. And it is for the same reason that automated PCa lesion segmentation based on artificial intelligence remains challenging to provide lesion segmentation to radiomics [43].

Our radiomics strategy based on the anatomical zones of the prostate has once again verified that the global characteristics of the prostate are significantly correlated with the pathological grading of prostate cancer [24, 44, 45]. We found that radiomics analysis based on biparametric MRI can effectively predict the ISUP score of prostate cancer, providing an important basis for personalized treatment plans. In real clinical practice, this method can improve the diagnostic workflow for prostate cancer, especially in terms of risk assessment before biopsy. Specifically, it can help clinicians determine whether patients need immediate surgery or further imaging tests, potentially reducing the rate of unnecessary biopsies. In addition, for ambiguous cases, the method provides a more accurate ISUP grade, which optimizes the patient's treatment strategy. By using a random forest model to comprehensively analyze imaging features, clinicians can not only guide individualized treatment, but also continuously monitor patients' imaging changes during

follow-up to detect tumors that may recur early, thereby further improving patient survival rates.

A total of 12,918 image-based features were extracted from T2WI, ADC, and DWI images of PZ and CG ROIs. In T2WI images, the prostate is typically visualized as two distinct zones: the CG, which includes the transition zone and central zone, and the peripheral zone (PZ). Our focus on segmenting the PZ and CG aligns with current clinical practices and enables more stable and reliable prostate segmentation [46]. The PZ is of particular clinical significance, as it is the site where over 70% of prostate cancers (PCas) originate, making it a primary target for biopsy. In contrast, the incidence of PCas in the CG region (including the TZ and CZ) is less than 30% [47, 48]. Since LASSO regression is sensitive to outliers and cannot effectively model nonlinear relationships, this study employed a random forest regressor for feature selection. From this analysis, we identified 20 features associated with the ISUP grading of prostate cancer (PCa), 14 of them are from DWI, which is consistent with PI-RADS recommends DWI as the imaging sequence of choice for evaluating PZ lesions and determining the malignancy of transition zone lesions [8].

Despite the significance of the findings of this study, we must also acknowledge the challenges faced. First, the variability between multiple centers may affect the consistency and reliability of the data. Second, the standardization of imaging protocols is essential to ensure the reproducibility of results between different laboratories. Finally, the computational infrastructure required to implement the random forest model may limit its widespread application.

This study had some limitations. First, for some patients, clinical features such as prostate-specific antigen level, and prostate-specific antigen density could not be included in the prediction model, but they are commonly used by clinicians to assess the aggressiveness of PCa [49, 50]. Second, while the diagnostic performance of the combined model PZ+CG improved at ISUP grades 2–4, it slightly decreased at ISUP grades 1 and 5. This discrepancy may be attributed to the imbalanced distribution of categories within the multicenter dataset. Although this study utilized multi-center data, it was derived from a single dataset, which may introduce potential bias. To enhance the robustness and generalizability of the findings, future studies should incorporate external validation using independent datasets from different populations or institutions. Additionally, employing cross-validation techniques during model development could help mitigate overfitting and provide a more reliable assessment of the model's performance across diverse patient cohorts. Prospective studies based on these strategies are warranted to further validate the model's robustness and clinical applicability.

Conclusion

In conclusion, we demonstrated the promising performance of anatomical ROI-based radiomics models in predicting the ISUP grade of PCa using a large multi-center prostate cancer dataset, which may improve diagnosis and treatment workflows for prostate cancer.

Author contributions Yuying Liu: Project development, Data collection, Data analysis, Writing – original draft; Xueqing Han: Investigation, Writing – review & editing; Haohui Chen: Writing – review & editing; Qirui Zhang (Corresponding author): Project development, Supervision, Writing – review & editing.

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Data availability <https://pi-cai.grand-challenge.org/DATA/>.

Code availability Not applicable.

Declarations

Ethical approval Our study does not require Institutional Review Board or Health Insurance Portability and Accountability Act approval because we use public datasets.

Consent for Publication Not applicable.

Competing interests The authors declare no competing interests.

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