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Radiomics Assessment of Bladder Cancer Grade Using Texture Features from Diffusion-Weighted Imaging

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Abstract

Purpose—To 1) describe textural features from diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps that can distinguish low-grade bladder cancer from high-grade one, and 2) propose a radiomics-based strategy for cancer grading using texture features.

Materials and Methods—61 patients with bladder cancer (29 in high- and 32 in low-grade groups) were enrolled in this retrospective study. Histogram- and gray-level co-occurrence matrix (GLCM)-based radiomics features were extracted from cancerous volumes of interest (VOIs) on DWI and corresponding ADC maps of each patient acquired from 3.0T MR. Mann-Whitney U test was applied to select features with significant difference between low- and high-grade groups ($p < 0.05$). Then support vector machine with recursive feature elimination (SVM-RFE) and classification strategy was adopted to find an optimal feature subset and then to establish a classification model for grading.

Results—A total 102 features were derived from each VOI and among them, 47 candidate features were selected, which showed significant inter-group difference ($p < 0.05$). By the SVM-RFE method, an optimal feature subset including 22 features was further selected from candidate features. The SVM classifier using the optimal feature subset achieved the best performance in bladder cancer grading, with an area under the receiver operating characteristic curve, accuracy, sensitivity and specificity of 0.861, 82.9%, 78.4% and 87.1%, respectively.

Conclusion—Textural features from DWI and ADC maps can reflect the difference between low- and high-grade bladder cancer, especially those GLCM features from ADC maps. The

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proposed radiomics strategy using these features, combined with the SVM classifier, may better facilitate image-based bladder cancer grading preoperatively.

Keywords

Radiomics; Bladder Cancer Grade; Texture Feature; Support Vector Machine; Apparent Diffusion Coefficient

Introduction

Bladder cancer has become the fourth most common cancer among males (1). Tumor staging and histopathological grade are the most important prognostic factors (2-4). Although treatment selection is largely driven by tumor stage, cancer grade is also a factor in therapeutic and follow-up decisions, especially for non-muscle-invasive bladder cancer (NMIBC). The standard treatment for low-grade NMIBC is transurethral resection (TUR). However, according to National Comprehensive Cancer Network (NCCN) guideline for bladder cancer, if a high-grade NMIBC lesion is detected at the initial TUR, a second TUR should be performed for complete resection of lesion (5). For refractory lesions, cystectomy may be performed (4,5). Furthermore, fibroblast growth factor receptor 3 (FGFR3) mutations are closely associated with low-grade NMIBC (6). Thus, accurate grading of bladder cancer is important for describing tumors' biological behavior for prognosis and clinical decision.

The grade of bladder cancer is determined by pathological analysis of tumor samples according to World Health Organization (WHO) 2004 bladder cancer grading criteria (2). Noninvasive and accurate determination of the grade preoperatively would have an impact on clinical decision making, treatment selection and prognostication for patients with bladder cancer.

Anatomic MRI techniques have shown potential to determine tumor location and invasion (7), while functional MRI techniques, especially the diffusion-weighted (DW) imaging and associated apparent diffusion coefficient (ADC), have exhibited its capability in assessing biological behaviors such as cellularity (7-9) and demonstrated their usefulness in bladder cancer management, especially in grade assessment (10-17). Previous studies indicated an inverse correlation between ADC values and tumor grades, and the ADC value may in part predict the histologic grade of bladder cancer. Moreover, it has been reported that the ADC value is likely to be an imaging biomarker reflecting the biological aggressiveness of bladder cancer due to its correlation with Ki-67 labeling index, an established marker of cell proliferation (15). However, ADC values overlap between low- and high-grade tumors, making it somehow difficult to distinguish tumor grades accurately with ADC values alone (18). More distinctive image signatures, which could describe the diffusion pattern and heterogeneous distribution of tumor tissues in DW images and ADC maps, are in great need for bladder cancer grading.

Recently, the term *radiomics*, the extraction of multiple quantitative features from images has drawn attention (19). Several cancer-related radiomics studies suggested that some quantitative imaging descriptors (such as texture features derived from MRI) could provide

more information for cancer diagnosis (20-26). For example, Kang *et al.* (23-26) have demonstrated that texture features derived from histogram and the gray-level co-occurrence matrix (GLCM) of ADC maps can be effective for grading and prognostic analysis of gliomas. For bladder cancer, Shi and Xu *et al.* (20, 21) have observed that histogram and GLCM feature analysis of T2-weighted images showed significant difference between carcinomatous tissues and bladder wall. However, there is no clear consensus on the specific imaging signatures that are most effective in distinguishing the grading of bladder cancer.

Based on the above observations, we hypothesized that a radiomics strategy, which conjuncts texture-based image signatures, like histogram and GLCM textures derived from DW images and ADC maps, with machine learning-based classification using a support vector machine (SVM) classifier, could help to differentiate between the bladder cancer grades.

Materials and Methods

This retrospective study was approved by the ethics review board of our institution. The requirement for informed consent was waived because, as a noninvasive technique for patients with suspected bladder cancer, DW image acquisition was a part of the routine MRI protocol.

Patient Population

Seventy-four patients who were diagnosed as bladder cancer between October 2013 and December 2015 were collected for this study, as shown in Figure 1. Inclusion criteria were as follows: (a) patients with postoperative pathologically confirmed bladder cancer for the first time, and (b) undergone an initial MR scan with DW imaging protocol at a standard b value ($b = 0$ and 1000 sec/mm^2) prior to any treatment and operation. Among them, 13 patients were excluded owing to the following conditions that might influence textural features extracted from image data: (a) with lesions smaller than 5mm (11,14,15), and (b) with imaging artifacts making segmentation of cancer difficult (e.g. motion or susceptibility artifacts). Finally, 61 patients were eligible in this study and divided into low- and high-grade groups (32 low-grade and 29 high-grade) according to their pathological results.

Imaging Data Acquisition

All patients were scanned by a 3.0 T MR scanner (Discovery MR 750; GE Medical Systems) with a torso coil (8CH HD Torso Array, GE Healthcare Coil). DW images were acquired using a single shot echo-planar sequence in the axial plane ($b = 0$ and 1000 sec/mm^2); repetition/echo time, 3600/58.2ms; acquisition time, 90.873-97.228s; flip angle, 90° ; field of view, $37\text{cm} \times 37\text{cm}$; slice thickness, 5.5mm; slice number, 40; pixel size, $1.5625\text{mm} \times 1.5625\text{mm}$; matrix, 256×256).

Corresponding ADC maps were then calculated voxel by voxel using a custom-developed package of MATLAB R2012b (MathWork, Natick, Mass), by solving the following equation:

$$S(b_{1000})/S(b_0)=\exp(-b_{1000} \times \text{ADC}) \quad (1)$$

where $S(b_{1000})$ and $S(b_0)$ represent the signal intensity (SI) of a certain voxel in the presence and in the absence of diffusion sensitization, respectively. The slice size and number of ADC maps ($256 \times 256 \times 20$) were the same as that of DW images.

VOIs Delineation

In most previous studies, 2D regions of interests (ROIs) of cancerous tissues or other types of interested tissues were extracted from image slices and used for further analysis, making it quite difficult to reveal the heterogeneity of the entire lesion (18). In this study, instead of using ROIs, 3D VOIs of bladder tumors were extracted by stacking-up corresponding ROIs delineated slice by slice from each patient's dataset. All VOIs were delineated on DW images ($b=1000 \text{ sec/mm}^2$) and the contours of VOIs were copied to corresponding ADC maps, as shown in Part 1 of Figure 2.

The VOI delineation was carried out using a custom-developed package of MATLAB R2012b by two radiologists (G. C. and Q. T.) who had MRI interpretation experience of 23 years and 8 years, respectively. During the VOI delineation, to avoid variation, all tumor VOIs were first outlined by two readers independently, who were blinded to the information of tumor grades. Then they worked together on outlined contours of each patient via a consensus reading, with information from both T2 weight images and DWI.

Feature Extraction

Texture features derived from the GLCM, also called Haralick features, have been widely used in medical image analysis for their ability to characterize the spatial dependence of gray levels using the second-order statistics (21,23,27). In this study, histogram and GLCM features were extracted from cancerous VOIs on DW images and corresponding ADC maps, respectively. From each VOI, 9 histogram features and 42 GLCM features were derived. Therefore, total 102 features were extracted from both DWI and ADC maps, as shown in Part 2 of Figure 2 (Please refer to Supplementary Materials for details of feature description). To eliminate the effect of different feature ranges on the classification performance, all the feature values were normalized to a range of $[-1, 1]$.

Feature Selection and Classification using the SVM

Though 102 features were calculated for each tumor region, these features would not contribute equally to bladder cancer grading assessment. Features less capable of cancer grading or highly correlated to each other would make the classifier overtraining and poor testing outcome. To find features highly correlated with tumor grades, statistical analysis was first performed on all features to find a candidate feature set that has significant difference between low-grade and high-grade groups.

To further select features with higher distinguishing power on cancer grading, the SVM with recursive feature elimination (SVM-RFE) method (28, 29) was adapted. The selection

process involves backward elimination where in each iteration, the feature that had the least contribution on improving the performance of the classifier was removed. As the algorithm continued, all the features were removed and feature ranking was generated based on the number of iterations when the feature was discarded. The visualization of this process was depicted in Figure 3, the color of a feature represents its contribution in the differentiation task. The warmer the color is, the more it contributes. With the SVM-RFE, the unordered features were ranked from the most important one with red color to the least important one with the deep blue color. With the ranked features, different feature sets could be obtained by selecting *Top-n* features from the ordered sequence ($1 \leq n \leq N$). The set of first n features was fed into the SVM classifier, and its performance for differentiating low- and high-grade bladder cancer could be evaluated by ROC curve and the area under the curve (AUC). Finally, a subset with the highest AUC (containing the first n_p features) was selected as the optimal feature subset for the discrimination task.

To validate the hypothesis, five groups of features were selected and their performance on the discrimination of high-grade tumors from low-grade ones were evaluated: a) the ADC mean alone, a suggested biomarker for bladder cancer grading by averaging the ADC map (10, 11); b) the SI mean alone, another suggested histogram-based biomarker for bladder cancer detection derived from the DW image ($b=1000 \text{ sec/mm}^2$) (11); c) All the features used in this study, including those from DWI and those from corresponding ADC maps, respectively; d) The candidate feature set selected by the Mann-Whitney U test; and e) the optimal feature subset selected by the SVM-RFE ranking method. The widely-used LIBSVM package (30, 31) was adopted to perform the SVM classification task by using the four feature groups. The grid search method in the LIBSVM package was applied to search for the optimal parameter combination for each classifier. Then optimized classifier was trained and tested by a 100 round of 10-fold cross validation randomly to demonstrate its generalization and stability (30, 32). The average performance of each classifier was visualized by its ROC curve. The accuracy, sensitivity and specificity for cancer grading of each classifier were also calculated, as described in Part 3 of Figure 2.

Statistical Analysis

In this study, all the statistical analysis was performed using the IBM SPSS Statistics (version 17.0; SPSS; Chicago). The level of confidence was kept at 95% and results with P values less than 0.05 considered to be significant. First, the Student's t test was applied to test whether inter-group differences in age and tumor size existed between the low- and high-grade groups of patients. Chi-square test was used to find if the constituent ratio of sex and tumor staging was significantly different between groups. Then the Mann-Whitney U test was applied on all features to find those with significant inter-group difference. ROC curve analysis was performed to calculate the AUC and corresponding 95% confidence interval.

Results

According to the statistical results on characteristics of 61 patients (29 high-grade and 32 low-grade patients) listed in Table 1, the mean age of patients with high-grade bladder

cancer was significantly higher than that of low-grade group ($p<0.05$). Furthermore, the constituent ratio of NMIBC and MIBC patients in low- and high-grade groups was significantly different ($p<0.05$). No significant difference was found in gender and tumor size of two groups.

With Mann-Whitney U test, 47 out of 102 features showed significant inter-group difference ($p<0.05$) between the low- and high-grade groups of bladder cancer, and were determined as the candidate feature set for further analysis. The composition ratio of the candidate feature set was listed in Table 2. Among them, 43 (91.5%) were GLCM features and 4 were histogram features. Especially, as one of the histogram features, the mean ADC value of low-grade samples was significant higher than that of high-grade ones ($p<0.05$), which was consistent with the observation of previous studies. However, there was no significant inter-group difference ($p=0.583$) in mean SI value of the DW image ($b=1000 \text{ sec/mm}^2$).

Based on the candidate feature set, SVM-RFE was performed and feature selection process using ranking features is depicted in Figure 4. Comparing with other feature subsets, the subset containing the first 22 features achieved the highest AUC with minimal number of features and therefore was considered as the optimal one.

Table 2 also lists the composition ratio of the optimal feature subset. Among 22 optimal features, 18 were GLCM features and 4 were histogram, while 18 came from ADC maps and 4 from DWI ($b=1000 \text{ sec/mm}^2$). Comparing the feature groups of two feature subsets, it can be observed that 4 histogram features from ADC maps kept unchanged (i.e., mean, median, trimmed mean and mode). However, the number of GLCM features from DWI reduced greatly from 19 to 4 in the optimal subset. The top-3 features in the subset were the *contrast* of GLCM ($d=3$) from ADC map, the *median* of ADC map, and the *entropy* of GLCM ($d=1$) from DWI (Please refer to Supplementary Materials for details of feature names).

The normalized feature value distribution of the optimal subset for patients with low- and high-grade bladder cancer is visualized as a heat map in Figure 5. For a certain feature (F_n), its value ranged from -1 to 1 and was represented by different colors when changed across patients. The warmer the color is, the larger the value is. Though the value distribution patterns of features were intuitively different between patients with low- and high-grade bladder cancer, it was quite difficult to find an explicit cutoff value for each feature to accurately separated high-grade cancer from low-grade ones. Therefore, a SVM classifier using the optimal feature subset was used to build the prediction model for cancer grading.

The performance and ROC curves of different feature subsets for bladder cancer grading are depicted in Table 3 and Figure 6(a). The P values of the ROC curves analysis listed in the rightmost column suggest that, except for the SI mean feature ($p=0.152$), classification results using other feature subsets were all significantly effective for bladder cancer grading ($p<0.01$). Furthermore, the grading performance using features from ADC map was more effective than using features from DWI. The best performance for cancer grading was achieved by using the optimal feature subset, with accuracy, sensitivity, specificity and AUC of 82.9%, 78.4.5%, 87.1% and 0.861, respectively. The performance of 4 histogram features

and 18 GLCM features in the optimal subset, is depicted in Figure 6 (b). Corresponding AUC and accuracy were 0.662, 63.7% and 0.820, 80.2%, respectively.

Discussion

Recent studies (11, 13-17) have indicated differences in ADC value in cancer grades, which was also validated in our study. However, we found the grading performance using the candidate or optimal features was improved, compared to using the ADC value alone. This indicates the discriminative power of GLCM and histogram features. Moreover, the classification performance using the optimal feature subset selected by SVM-RFE outperforms that using the candidate feature set. This reveals the important role of feature selection in a radiomics-based strategy. In contrast, the grading performance only using the SI mean of DWI was poor. It's reasonable because SI would be a tool for differentiating the lesion from peritumoral tissues rather than describing intra-tumor characteristics. It was mostly used for bladder cancer detection and staging, rather than grading (11).

By analyzing the optimal feature subset, 18 out of 22 features were from GLCM and the grading performance using 18 GLCM features was much better than that of the other 4 histogram features. Theoretically, GLCM features can describe the contrast, complexity and heterogeneity of local intensity patterns, and potentially have more discriminative power cancer grading. On the other hand, the grading performance using all ADC features was better than that using all DWI features. Considering that cancer of different pathological grades would have different diffusion patterns of water molecules, different image phenotypes may be better presented in ADC maps. The top-3 discriminative features in the optimal feature subset were the GLCM *contrast* of the ADC map, the median of the ADC map, and the GLCM *entropy* of DWI, respectively. All these results suggest that GLCM features of the ADC map seem more important for accurate assessment of bladder cancer grades. Histogram features of the ADC map also play a certain role in grading, which has been suggested by other studies, and should not be neglected.

The novelty of this study can be summarized as following: 1) Textural features extracted from diffusion distributions were used for bladder cancer grading. 2) An optimal feature set was found with favorable discriminative power on cancer grading. 3) A novel and noninvasive radiomics grading strategy was proposed for prediction of bladder cancer grade preoperatively.

There are still some limitations in this study. First, it is a retrospective study with a small sample size of 61 patients, a model validation using a separated cohort for the established SVM classifier cannot accomplish. In addition, all DW images were acquired by the same scanner at a single institution with the same imaging protocols, which reduced the generalization of the classification model. Future validation with multi-institutional large datasets would benefit greatly. Second, although we found GLCM features of ADC maps were valuable for bladder cancer grading, ADC values used in this study were derived from a mono-exponential diffusion model, as described in equation (1). Recent studies using a bi-exponential or a stretched exponential diffusion model have shown that some other effective parameters, such as D , D^* and f , also performed well in cancer grading (33, 34). Moreover,

Kwak *et al.* (26) indicated that texture features extracted from high-b-value DWI ($b=2000$ sec/mm²) showed better performance in automated benign and malignant diagnosis of prostate lesions. Therefore, features of other parameter maps derived from DW images using the bi-exponential, stretched-exponential diffusion model or high-b-value will be considered in our future work for bladder cancer grading. Besides, the population biases in this retrospective study should be considered and improved in the future work.

In conclusion, textural features extracted from ADC maps and DWI can statistically reflect the difference between low- and high-grade tumors. The feature subset selected from these features, especially some GLCM features from ADC maps, may be potential imaging biomarkers for the grading of bladder cancer noninvasively and efficiently. To sum up, the proposed radiomics strategy using histogram and GLCM texture features from DW images and ADC maps, combined with SVM classifier, may better facilitate image-based bladder cancer grading preoperatively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Flow diagram for patient selection.

Figure 2.
The schematic diagram of the proposed radiomics strategy for bladder cancer grading.

Figure 3.
The process for finding the optimal feature subset by SVM-RFE.

Figure 4.
Classification performance using different subsets of ranking features.

Figure 5.
The heat map for normalized feature value distribution of the optimal subset (22 features) between low- and high-grade groups.

Figure 6. ROC curves of SVM classifiers using (a) six different feature sets and b) different features in the optimal feature subset.

Table 1
Baseline demographics and clinical characteristics of patients

Characteristic	Low Grade	High Grade	P value
Patients (N/%)	32/61(52.5%)	29/61(47.5%)	
Gender			0.849
Male (N/%)	26/32(81.3%)	23/29(79.3%)	
Female (N/%)	6/32(18.7%)	6/29(20.7%)	
Age(Mean±SD)	59.8±11.7	66.9±9.7	<0.05*
Tumor Size (Mean ± SD)	5.8±9.4 cm ³	7.0±7.7 cm ³	0.596
Staging Status			<0.05*
NMIBC (N/%)	19/32(59.4%)	9/29(31.0%)	
MIBC (N/%)	9/32(28.1%)	18/29(62.1%)	
Missing	4/32(12.5%)	2/29(6.9%)	

Footnote: SD, standard deviation; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer.

Table 2
Feature compositions of the candidate feature set and the optimal feature subset

	Candidate Feature Set			Optimal Feature Subset		
	GLCM features	Histogram features	Constituent Ratio	GLCM features	Histogram features	Constituent Ratio
ADC map	24	4	59.6% (28/47)	14	4	81.8% (18/22)
DWI	19	0	19/47 (40.4%)	4	0	18.2% (4/22)
Constituent Ratio	91.5% (43/47)	8.5% (4/47)	100% (47/47)	81.8% (18/22)	18.2% (4/22)	100% (22/22)

Footnote: Numbers in parentheses are the data used to calculate percentages. **DWI**, diffusion-weighted image; **ADC**, apparent diffusion coefficient; **GLCM**, gray-level co-occurrence matrix.

Table 3
The classification performance of the SVM classifier using different feature subsets

Feature Group	Accuracy	Sensitivity	Specificity	AUC	95% Confidence Intervals	P value
Optimal feature subset (22 features)	82.9% (51/61)	78.4% (23/29)	87.1% (28/32)	0.861	[0.851, 0.870]	<0.01[*]
Candidate feature set (47 features)	78.6% (48/61)	72.5% (21/29)	84.1% (27/32)	0.841	[0.830, 0.861]	<0.01[*]
Features from ADC maps (51 features)	77.8% (47/61)	76.7% (22/29)	78.9% (25/32)	0.828	[0.818, 0.839]	<0.01[*]
ADC mean (1 feature)	67.2% (41/61)	60.7% (18/29)	73.1% (23/32)	0.675	[0.661, 0.689]	<0.01[*]
Features from DWI (51 features)	74.6% (46/61)	79.3% (23/29)	70.3% (23/32)	0.796	[0.785, 0.807]	<0.01[*]
SI mean (1 feature)	50.7% (31/61)	45.1% (13/29)	55.8% (18/32)	0.518	[0.504, 0.532]	0.152
All the Features (102 features)	74.0% (45/61)	74.0% (21/29)	73.9% (24/32)	0.805	[0.795, 0.817]	<0.01[*]

Footnote:

^{*} Results with *P* values less than 0.05 were considered to be significant. **SVM**, support vector machine; **DWI**, diffusion-weighted image; **ADC**, apparent diffusion coefficient; **SI**, signal intensity; **AUC**, area under curve.