Texture Analysis of Apparent Diffusion Coefficient Maps in Cervical Carcinoma: Correlation with Histopathologic Findings and Prognosis

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Purpose: To determine the feasibility of texture analysis of apparent diffusion coefficient (ADC) maps and to assess the performance of texture analysis and ADC to predict histologic grade, parametrial invasion, lymph node metastasis, International Federation of Gynecology and Obstetrics (FIGO) stage, recurrence, and recurrence-free survival (RFS) in patients with cervical carcinoma.

Materials and Methods: This retrospective study included 58 patients with cervical carcinoma who were examined with a 1.5-T MRI system and diffusion-weighted imaging with b values of 0 and 1000 sec/mm². Software with volumes of interest on ADC maps was used to extract 45 texture features, including higher-order texture features. Receiver operating characteristic (ROC) analysis was performed to compare the diagnostic performance of ADC map random forest models and of ADC values. Dunnett test, Spearman rank correlation coefficient, Kaplan-Meier analyses, log-rank test, and Cox proportional hazards regression analyses were also used for statistical analyses.

Results: The ADC map random forest models showed a significantly larger area under the ROC curve (AUC) than the AUC of ADC values for predicting high-grade cervical carcinoma (P = .0036), but not for parametrial invasion, lymph node metastasis, stages III–IV, and recurrence (P = .0602, .3176, .0924, and .5633, respectively). The random forest models predicted that the mean RFS rates were significantly shorter for high-grade cervical carcinomas, parametrial invasion, lymph node metastasis, stages III–IV, and recurrence (P = .0405, < .0001, .0344, .0001, and .0015, respectively); the random forest models for parametrial invasion and stages III–IV were more useful than ADC values (P = .0018) for predicting RFS.

Conclusion: The ADC map random forest models were more useful for noninvasively evaluating histologic grade, parametrial invasion, lymph node metastasis, FIGO stage, and recurrence and for predicting RFS in patients with cervical carcinoma than were ADC values.

Supplemental material is available for this article.

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Among women worldwide, the second most common gynecologic malignant neoplasm and the third most common cause of cancer death is cervical carcinoma (1). The main histologic types of cervical carcinoma, squamous cell carcinoma and adenocarcinoma, account for approximately 75% and 15% of all cervical cancers, respectively (2–4). The International Federation of Gynecology and Obstetrics (FIGO) stage, histologic type and grade, parametrial invasion, lymph node metastasis, and tumor diameter are important prognostic indicators of cervical carcinoma (2–6). Selecting and planning optimal treatment and predicting recurrence-free survival (RFS) depend on accurate preoperative assessment of these factors in patients with cervical carcinoma.

To evaluate the aggressiveness of cervical carcinoma, including parametrial invasion, lymph node metastasis, and distant metastasis, MRI is widely used (7), but accurate preoperative assessment of these prognostic factors is often difficult. Although the histologic grade of cervical carcinoma correlates with these prognostic factors and provides critical information for selecting treatment plans, accurate evaluation of the histologic grade of cervical carcinoma without an invasive biopsy remains challenging (8–10). Previous studies have reported the potential use of apparent diffusion coefficient (ADC) to predict the cervical carcinoma’s histologic grade; however, the differentiation of cervical carcinoma histologic grades based on ADC alone was reported to be difficult because ADC values overlap considerably among histologic grades (8–10). The diagnosis of cervical carcinoma always requires histologic confirmation, as it provides an evaluation on fundamental prognostic factors such as grading, infiltration, and possible correlation with viruses and oncogenes. However, the procedure of biopsy entails sampling errors due to its only piecemeal resection, as
Well as complications due to its invasiveness. Thus, noninvasive and more accurate pretreatment diagnosis techniques of cervical carcinoma histologic grade is desirable for patients with cervical carcinoma.

Texture analysis of cross-sectional images has recently been used for different cancers, and its clinical feasibility for tumor detection, tumor characterization, histologic grade assessment, and prediction of prognosis has been reported (11,12). Texture features of tumors reflect intratumoral heterogeneity, and tumors with higher heterogeneity are reportedly more aggressive and have poorer prognoses in many types of cancers (11–14). However, to the best of our knowledge, few reported studies have assessed the texture analysis of ADC maps for predicting the histologic grade and RFS in patients with cervical carcinoma (15–18).

Therefore, we aimed to assess the texture analysis of ADC maps as a noninvasive method for evaluating the most important prognostic indicators, which are the histologic grade of cervical carcinoma, parametrial invasion, lymph node metastasis, FIGO stage, and recurrence, and RFS prediction in patients with cervical carcinoma. Overall, we found that texture analysis of ADC maps correlated with cervical carcinoma grades and predicted high-grade cervical carcinoma, and texture analysis random forest models predicted stratified survival responses for multiple tumor characteristics. Taken together, our findings suggest that texture analysis could be developed as a noninvasive prognostic method for cervical carcinoma.

Materials and Methods

Study Design

Our institutional review board approved this retrospective study and waived the requirement for written informed consent. Between September 2010 and August 2017, we evaluated 58 consecutive female patients with histologically confirmed cervical carcinoma who were treated at our institution. Patient age at the time of MRI ranged from 28 to 83 years (mean age, 57.9 years ± 15.0 [standard deviation]). All patients underwent pretreatment MRI, including diffusion-weighted imaging (DWI). On the basis of the clinical and imaging findings, the patients were subsequently assigned to treatment with primary surgery (n = 28), radiation therapy (n = 14), or concurrent chemoradiation therapy (n = 16) (Table 1). There was no overlap in study participants from previous studies.

MRI Technique

DWI was performed with a 1.5-T MRI system (Signa HDxt; GE Healthcare, Waukesha, Wis) equipped with actively shielded gradients that had a maximum strength of 33 mT/m. An eight-channel phased-array body coil was used for all measurements.

DWI data were obtained in the axial plane by using a spin-echo–based single-shot echo-planar imaging sequence with the following parameters: repetition time msec/echo time msec, 4500/78.2; field of view, 340 × 340 mm; matrix, 128 × 128; section thickness, 6 mm with a 1.2-mm intersection gap; b values, 0 and 1000 sec/mm²; motion-probing gradients in three orthogonal directions; and number of signals acquired (NSA), 4. The acquisition time for the DWI sequence was 1 minute 17 seconds.

The standard MRI protocol for patients with cervical carcinoma at our institution included axial DWI (as mentioned above), axial three-dimensional (3D) T2-weighted imaging (2000/121.55; field of view, 340 × 340 mm; matrix, 256 × 224; section thickness, 2.4 mm without a gap; NSA, 2), sagittal T1-weighted imaging (140/4.2; section thickness, 6 mm with a 1.2-mm gap; NSA, 1), sagittal T2-weighted imaging (3500/87.384; section thickness, 6 mm with a 1.2-mm gap; NSA, 2), and axial 3D T1-weighted imaging in dual echoes (7.048/2.1 and 4.5; section thickness, 2.4 mm without a gap; NSA, 1). After an intravenous bolus injection of 0.1 mmol gadobutrol per kg of body weight (Gadovist; Bayer Yakuhin, Osaka, Japan), we also performed sagittal triple-phase 3D dynamic contrast material–enhanced imaging (3/2/1.768; section thickness, 3 mm without a gap; NSA, 1), axial contrast-enhanced 3D T1-weighted imaging (4.696/2.268; section thickness, 2.4 mm without a gap; NSA, 1), and axial contrast-enhanced 3D T1-weighted imaging in phase (6.148/4.2; section thickness, 2.4 mm without a gap; NSA, 1).

We used different section thicknesses between the T2-weighted imaging (2.4 mm) and DWI (6 mm) because the T2-weighted images were obtained with a 3D sequence and the diffusion-weighted images were obtained with a 2D sequence. However, this did not affect the results of texture analysis in our study because texture analysis was performed only for ADC maps and

Abbreviations

ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristic curve, DWI = diffusion-weighted imaging, FIGO = International Federation of Gynecology and Obstetrics, NSA = number of signals acquired, RFS = recurrence free survival, ROC = receiver operating characteristic, ROI = region of interest, 3D = three dimensional

Summary

Texture analysis of apparent diffusion coefficient maps provided useful information for noninvasively evaluating the histologic grade of cervical carcinoma, parametrial invasion, lymph node metastasis, International Federation of Gynecology and Obstetrics stage, and recurrence and for predicting recurrence-free survival in patients with cervical carcinoma.

Key Points

- Random forest estimates using texture features from apparent diffusion coefficient (ADC) maps positively correlated with grades 1–3 cervical carcinomas.
- High-grade cervical carcinomas had significantly higher areas under the receiver operating characteristic curve using texture analysis of ADC maps compared with apparent diffusion coefficients.
- The ADC map random forest models predicted that the mean recurrence-free survival (RFS) was significantly shorter for high-grade cervical carcinomas, parametrial invasion, lymph node metastasis, stages III–IV, and recurrence.
- The ADC map random forest models for parametrial invasion and stages III–IV were more useful than ADC values for predicting RFS in patients with cervical carcinoma.
T2-weighted imaging was used only as reference. In addition, only two, instead of three, \( b \) values (0 and 1000 sec/mm\(^2\)) were included in our study because of its retrospective nature; however, the \( b \) values of 0 and 1000 sec/mm\(^2\) were a standard combination for ADC maps in many previous studies (7–10). Furthermore, high \( b \) values (1500 or 2000 sec/mm\(^2\)) seemed to cause severe susceptibility artifacts on diffusion-weighted images and ADC maps, although they might generate an adequate ADC map to obtain more reliable results of texture analysis.

### Image Processing

The ADC (in \( 10^{-3} \) millimeters squared per second) for each voxel was calculated from isotropic diffusion-weighted images with \( b \) values of 0 and 1000 sec/mm\(^2\) by calculating the slope of the logarithmic decay curve for signal intensity against the \( b \) value, according to the equation \( S = S_0 \cdot \exp(-b \cdot \text{ADC}) \). Finally, we used corresponding ADC values on a pixel-by-pixel basis to generate ADC maps. The standard software built into the MRI unit (Signa HDxt; GE Healthcare) was used for all image processing. No specific postprocessing other than the standard software built into the MRI unit was performed for the postprocessing steps.

### LIFEEx

LIFEEx software (version 4.00; Inserm, Orsay, France) (19,20) was used to quantitatively assess cervical carcinoma heterogeneity. LIFEEx is freeware for texture analysis that can be found at www.lifexsoft.org. We could not indicate the equations and documented code, or pre-extraction filters used for the LIFEEx software, because the codes are proprietarily owned and are not accessible to the public. However, all the features were implemented according to the current version of the Image Biomarker Standardization Initiative guidelines (21). Regions of interest (ROIs) were drawn around the visible tumor on all ADC maps where the tumor was seen, with diffusion-weighted images, T2-weighted images, and dynamic contrast-enhanced images used as references to ensure complete tumor coverage. Two observers (I.Y. and N.M., with 26 and 22 years of experience in reading MR images, respectively), who were aware of the cervical carcinoma diagnoses but blinded to the histopathologic results and clinical outcomes of the patients, manually drew the ROIs on each tumor by consensus. Disagreements on any findings were resolved by discussion and reaching a consensus. The tumor contour was defined as low-signal-intensity areas on ADC maps, as high-signal-intensity areas on diffusion-weighted images, as intermediate-signal-intensity areas in the low-signal-intensity cervix on T2-weighted images, and as high-signal-intensity areas in the low-signal-intensity cervix on dynamic contrast-enhanced images. To prevent affecting the texture of the tumor by volume averaging, the ROIs were drawn to avoid the tumor’s peripheral border. After segmenting the tumors, we used LIFEEx to calculate 45 texture features (19–21).

The texture features were calculated for each volume of interest: four statistical indexes (mean, minimum, maximum, and standard deviations of gray levels); five first-order histogram features (skewness, kurtosis, entropy_log10, entropy_log2, and energy); 32 higher-order features from the gray-level co-occurrence matrix, the neighborhood gray-level different matrix, the gray-level run length matrix, and the gray-level zone length matrix; and four shape indexes (sphericity, compactness, volume/mL, and volume_voxels). A detailed description of each texture feature is available in the LIFEEx technical appendix (20). We performed feature calculation by using the following specific settings: (a) spatial resampling, using 2.0 \( \times \) 2.0 \( \times \) 2.0 mm for spacing; (b) intensity discretization, using 64 gray levels; and (c) intensity rescaling, using the 64 gray levels between the absolute minimum and maximum values in the volume of interest (19,20).

### Table 1: Patient and Tumor Characteristics

| Variable                             | Data (n = 58) |
|--------------------------------------|---------------|
| Age (y)*                             | 57.9 ± 15.0 (28–83) |
| FIGO stage                           |               |
| IB1                                  | 23 (39.7)     |
| IB2                                  | 2 (3.4)       |
| IIA1                                 | 5 (8.6)       |
| IIB                                  | 14 (24.1)     |
| IIA                                   | 1 (1.7)       |
| IIB1                                 | 7 (12.1)      |
| IVA                                  | 3 (5.2)       |
| IVB                                  | 3 (5.2)       |
| Histologic subtype                   |               |
| Squamous cell carcinoma              | 47 (81.0)     |
| Adenocarcinoma                       | 8 (13.8)      |
| Small cell carcinoma                 | 3 (5.2)       |
| Histologic grade                     |               |
| Low grade (grades 1 and 2)           | 26 (44.8)     |
| High grade (grade 3 and small cell carcinoma) | 32 (55.2) |
| Parametrial invasion                 |               |
| Absence                              | 31 (53.4)     |
| Presence                             | 27 (46.6)     |
| Lymph node metastasis                |               |
| Absence                              | 45 (77.6)     |
| Presence                             | 13 (22.4)     |
| Definitive therapy                   |               |
| Surgical treatment                   | 28 (48.3)     |
| RT/CCRT                              | 30 (51.7)     |
| Recurrence                           |               |
| Absence                              | 42 (72.4)     |
| Presence                             | 16 (27.6)     |

Note.—Unless otherwise noted, data are number of patients with percentages in parentheses. CCRT = concurrent chemoradiation therapy. FIGO = International Federation of Gynecology and Obstetrics. RT = radiation therapy.

* Data are mean values ± standard deviations with the range in parentheses.
On the basis of a recent article analyzing the limitations of texture analysis by Varghese et al (12), we followed the summary chart as taken from this report evaluating the need for more uniform reporting of multiple aspects of texture analysis studies (See table 2: Checklist of Suggested Attributes in Future Radiomics Studies in [12]). For our study, which is a pilot study with use of radiomic feature as the metric in predicting disease type or treatment outcome, it would be ideally necessary to have a measurement reliability check and a control for multiple testing errors (12). In this respect, we included the first-order texture features, including the data skewness, in our study because they are less subject to error than the second-order texture features.

In addition, ROIs, which were approximately equal in size to the uterine cervix wall layer thickness, were drawn on the uterine cervix wall layers on ADC maps. The mean values of three or four ROIs were calculated for each uterine cervix wall layer for comparison with the cervical carcinomas.

**Histologic Preparation and Examination**

After surgery \((n = 28)\) or biopsy \((n = 30)\), each specimen was subjected to histopathologic examination. Tissues were paraffin embedded and cut into 3-µm-thick slices on a microtome, and the sections were stained with hematoxylin-eosin. After staining, one pathologist (D.K., with 19 years of experience in histopathology), who was blinded to the MRI results, examined all specimens to assess the layers of the uterine cervix wall and to evaluate the histologic type and histologic grade, parametrial invasion, lymph node metastasis, and FIGO stage. According to the FIGO system criteria (2,22), the pathologist classified the cervical carcinomas into three histologic types: squamous cell carcinoma, adenocarcinoma, or other cervical carcinoma type. Squamous cell carcinoma and adenocarcinoma were classified into three histologic grades: grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated). Further, we combined grade 1 and grade 2 cervical carcinomas into “low-grade tumors” and grade 3 cervical carcinomas and other type cervical carcinomas into “high-grade tumors.”

**Statistical Analysis**

We used a random forest method to build a diagnostic model for predicting high-grade cervical carcinomas, parametrial invasion, lymph node metastasis, stages III–IV, and recurrence in patients with cervical carcinoma. This method involves combining multiple classification and regression trees that are independent diagnostic algorithms (23–26). To build the most accurate diagnostic model for each outcome, we used XLSTAT software (version 2018.7; Addinsoft, New York, NY). XLSTAT is commercially available software for machine learning that can be found at www.xlstat.com. The software generated and evaluated 500 models by varying the 45 parameters in the random forest model, trying different feature sets, and then selecting the best-performing model. To ensure the final model’s robustness and to avoid potential data overfitting, all models were
cross-validated by using the leave-one-out method. The random forest model separated the samples into a boot-strapped sample and an out-of-bag sample and then used the error in the out-of-bag sample as an internal cross-validation. From the internal cross-validation with the out-of-bag error estimate, we computed the area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, specificity, and accuracy of the final models. Feature importance was calculated as the percentage increase in the misclassification rate when that feature’s values were permuted, compared with the misclassification rate when they were left intact. In the model building, we removed the variables that did not contribute to the diagnosis for each outcome or that were highly correlated with other features.

The means ± standard deviation of the ADC values of the uterine cervix wall layers and the cervical carcinomas were calculated from ADC maps. Differences in ADC values between the uterine cervix wall layers and cervical carcinomas were analyzed by Dunnett test. Correlations between ADC values and the histologic grades of cervical carcinomas were assessed by Spearman rank correlation coefficient.

The ROC curve analyses were used to assess the usefulness of the random forest model and ADC values for predicting high-grade cervical carcinomas, parametrial invasion, lymph node metastasis, stages III–IV, and recurrence in patients with cervical carcinoma. In ROC curve analyses, the optimal thresholds of the random forest model and of ADC values were determined as the values that would maximize the average sensitivity and specificity. We performed all tests on the same set of patients and obtained all the comparisons (and all the P values) from tests performed on the same set of patients, instead of on independent samples. For comparisons with correlated data, we used the method of DeLong et al (27) to compare the areas under correlated ROC curves.

Kaplan-Meier analyses were used to estimate survival rates. Recurrence was defined as local, regional lymph nodal, and distant after treatment in the study population. The event time was calculated as the time between the date of treatment and date of recurrence in applicable patients. One patient was censored due to death from other cause (subarachnoid hemorrhage) and other stable patients were censored at the last available follow-up date. Associations of the random forest model and ADC values with RFS were analyzed by performing the log-rank test, top few principal components used as predictors in the logistic regression.

XLSTAT (version 2018.7), R (The R packages; R Development Core Team [2008], Vienna, Austria; www.r-project.org), IBM SPSS Statistics (version 25; IBM SPSS Japan, Tokyo, Japan), and MedCalc (version 17.9.7; MedCalc Software, Ostend, Belgium) were used to analyze the data. A P value < .05 was considered statistically significant in all analyses.

**Results**

**Patient, Tumor, and ADC Characteristics of the Cervical Carcinomas**

A total of 58 patients with histologically confirmed cervical carcinoma were enrolled in this study. Patient and tumor characteristics are found in Table 1. The histologic subtypes were squamous cell carcinoma in 47 (81.0%) patients, adenocarcinoma in eight (13.8%) patients, and small cell carcinoma in three (5.2%) patients. We combined grade 1 and grade 2 cervical carcinomas into “low-grade tumors” and grade 3 cervical carcinomas and other type cervical carcinomas into “high-grade tumors,” and thus there were only two histologic groups including 26 (44.8%) low-grade tumors and 32 (55.2%) high-grade tumors for texture analysis in our study. It is recommended that there should be at least 10 patients analyzed per histologic group to be able to predict grade (28), and our groupings met this criterion. In addition, 27 (46.6%) patients had parametrial invasion and 13 (22.4%) had lymph node metastases. On the basis of the FIGO system, 44 (75.9%) patients had stages I–II and 14 (24.1%) had stages III–IV.

All 58 (100%) cervical carcinoma tumors had lower ADC values than the normal uterine cervix wall layers, including the cervical mucosa, fibrous stroma, outer stroma, and parametrium (P < .0001 for all; Fig 1, Table 2). All 58 cervical carcinoma tumors were clearly depicted as hypointense areas on ADC maps and as hyperintense areas on diffusion-weighted images, so the ADC maps and DW images could clearly demarcate cervical carcinomas from the normal uterine cervix wall.

The ADC values of squamous cell carcinomas and adenocarcinomas were not significantly different (0.839 × 10⁻³ mm²/sec ± 0.091 vs 0.889 × 10⁻³ mm²/sec ± 0.143; P = .38), whereas the ADC values of small cell carcinomas (0.641 × 10⁻³ mm²/sec ± 0.109 vs 0.757 × 10⁻³ mm²/sec ± 0.184; P = .0002) and mean survival times and 95% confidence intervals were calculated. We also used Cox proportional hazards regression analyses for the random forest model and ADC values and calculated hazard ratio estimates and 95% confidence intervals.

In addition, to confirm the findings of the random forest model from ADC maps, we performed the following two simple analyses: (a) a logistic regression with forward-backward stepwise method for variable selection; and (b) principal component analysis on the features with the

Table 2: ADC Values of the Normal Uterine Cervix and Cervical Carcinomas

| Tissue                  | ADC Value (× 10⁻³ mm²/sec) | P Value |
|-------------------------|-----------------------------|---------|
| Cervical mucosa         | 1.614 ± 0.143               | < .0001 |
| Fibrous stroma          | 1.182 ± 0.120               | < .0001 |
| Outer stroma            | 1.743 ± 0.190               | < .0001 |
| Parametrium             | 2.578 ± 0.341               | < .0001 |
| Cervical carcinoma      | 0.835 ± 0.109               | NA      |

Note.—Data are mean values ± standard deviations. P value represents the differences in the ADC values between the normal uterine cervix wall layers and cervical carcinomas. ADC = apparent diffusion coefficient, NA = not available.
sec ± 0.095) were significantly lower than those of both ($P = .004$ and .001, respectively; Table 3). Although a significant inverse correlation was found between the ADC values and grades 1–3 ($r = -0.600, P < .0001$), there were no significant differences in ADC values between grades 2 and 3 for squamous cell carcinoma, adenocarcinoma, and cervical carcinoma ($P = .201, .201,$ and .072, respectively; Table 3). The ADC values of high-grade cervical carcinomas were significantly lower than those of low-grade cervical carcinomas ($0.786 \times 10^{-3}$ mm$^2$/sec ± 0.080 vs 0.896 $\times 10^{-3}$ mm$^2$/sec ± 0.111; $P < .0001$; Table 3).

**Diagnostic Performance of the Random Forest Model of Texture Features**

Next we assessed the random forest analysis of texture feature importance for each of the five outcomes. Of the 45 features analyzed, 29 variables for high-grade tumor, 21 for parametrial invasion, 27 for lymph node metastasis, 25 for FIGO stage, and 21 for recurrence were removed in the final random forest models because they either did not contribute to the diagnosis or they adversely affected the diagnosis because they were so closely correlated with other features that there was an increase in the bias term of the error. Consequently, the random forest model included 16 features for high-grade tumor, 24 features for parametrial invasion, 18 features for lymph node metastasis, 20 features for FIGO stage, and 24 features for recurrence (Table 4 and Table E1[supplement]). The five random forest models shared different features; however, the rankings of these features and their feature importance from random forest analysis differed between the five models.

The random forest model for predicting high-grade tumor showed a significant positive correlation between random forest estimates and grades 1–3 cervical carcinomas ($r = 0.799, P < .0001$), and there were also significant differences in the random forest estimates between grades 2 and 3 cervical carcinomas ($0.184 \pm 0.300$ vs $0.898 \pm 0.181$; $P < .0001$; Fig 2a). Furthermore, the random forest estimates of the high-grade cervical carcinomas were significantly higher than those of the low-grade cervical carcinomas ($0.894 \pm 0.183$ vs $0.135 \pm 0.268$; $P < .0001$; Fig 2b).

The AUC for the random forest model for predicting high-grade cervical carcinomas ($0.952, P < .0001$) was significantly larger than the area of 0.5; thus, a cutoff value of greater than 0.538 seemed to be useful for differentiating high-grade and low-grade cervical carcinomas (Table 5, Fig 3a). Although the AUC for the ADC values ($0.814, P < .0001$) was also significantly larger than the area of 0.5, the AUC for the random forest model was significantly larger than that for the ADC values ($0.952$ vs $0.814; P = .0036$). Therefore, the random forest model from ADC maps was found to significantly improve the diagnostic performance for discriminating between high-grade and low-grade cervical carcinomas relative to the performance of the ADC values.

The AUC for the random forest model was also significantly larger than the area of 0.5 for predicting parametrial invasion ($0.724, P = .0011$; cutoff $> 0.592$), lymph node metastasis ($0.651, P = .0368$; cutoff $> 0.024$), stages III–IV ($0.787, P < .0001$; cutoff $> 0.293$), and recurrence ($0.753, P < .0008$; cutoff $> 0.302$) (Table 5, Fig 3b–e). The AUCs for these random forest models were larger than the AUCs for the ADC values ($0.503, 0.520, 0.580,$ and 0.707, respectively), although these differences were not significant ($P = .0602, .3176, .0924,$ and .5633, respectively). Therefore, the random forest model from ADC maps was found to have higher (though not significantly higher) diagnostic performance than that of the ADC values for predicting parametrial invasion, lymph node metastasis, stages III–IV, and recurrence in patients with cervical carcinoma.

In addition, when we used the logistic regression with forward-backward stepwise method for variable selection, the respective AUCs were as follows: high-grade tumor,

| Table 3: ADC Values for Different Histologic Types and Grades of Cervical Carcinomas |
|---------------------------------|-----------------|----------------|
| Histologic Type and Grade       | ADC Value ($\times 10^{-3}$ mm$^2$/sec) | $P$ Value |
|---------------------------------|----------------------------------------|-----------|
| Squamous cell carcinoma ($n = 47$) | $0.839 \pm 0.091$ | < .0001, ($r = -0.600$) |
| Grade 1 ($n = 5$) | $1.010 \pm 0.057$ | |
| Grade 2 ($n = 15$) | $0.843 \pm 0.082$ | |
| Grade 3 ($n = 27$) | $0.804 \pm 0.060$ | |
| Adenocarcinoma ($n = 8$) | $0.889 \pm 0.143$ | .008, ($r = -0.849$) |
| Grade 1 ($n = 2$) | $1.093 \pm 0.037$ | |
| Grade 2 ($n = 4$) | $0.857 \pm 0.044$ | |
| Grade 3 ($n = 2$) | $0.751 \pm 0.105$ | |
| Small cell carcinoma ($n = 3$) | $0.641 \pm 0.095$ | NA |
| Cervical carcinoma ($n = 58$) | $0.853 \pm 0.109$ | < .0001, ($r = -0.600$) |
| Grade 1 ($n = 7$) | $1.034 \pm 0.064$ | |
| Grade 2 ($n = 19$) | $0.846 \pm 0.075$ | |
| Grade 3 ($n = 29$) | $0.801 \pm 0.063$ | |
| Small cell carcinoma ($n = 3$) | $0.641 \pm 0.095$ | NA |
| Cervical carcinoma ($n = 58$) | $0.835 \pm 0.109$ | < .0001 |
| Low-grade tumor ($n = 26$) | $0.896 \pm 0.111$ | |
| High-grade tumor ($n = 32$) | $0.786 \pm 0.080$ | |

Note.—Data are mean values ± standard deviations. $P$ value represents the correlation between ADC values and histologic grades of cervical carcinomas. ADC = apparent diffusion coefficient. Grade 1 = well differentiated, grade 2 = moderately differentiated, grade 3 = poorly differentiated. NA = not available.
### Table 4: Random Forest Models of Texture Features for Predicting Outcomes

| Feature          | Recurrence | Lymph Node Metastasis | Stages III–IV | Parametrial Invasion |
|------------------|------------|-----------------------|---------------|---------------------|
| **Selected Feature** | **Importance** | **Importance** | **Importance** | **Importance** |
| Histogram_Entropy | 10.715      | 7.067                 | 11.109        | 13.715              |
| Shape_Compatibility | 11.109     | 3.354                 | 5.714          | 4.278               |
| Histogram_Kurtosis | 3.532        | 2.936                 | 4.964          | 2.836               |
| GLZLM_GLNU | 6.746      | 2.614                 | 3.932          | 1.184               |
| NGLDM_Coarseness | 9.652      | 5.714                 | 6.660          | 8.662               |
| GLCM_Contrast | 7.067      | 2.936                 | 3.354          | 2.836               |
| GLRLM_RLNU | 6.746      | 2.614                 | 3.932          | 1.184               |
| GLZLM_GLNU | 13.110     | 7.067                 | 2.936          | 2.836               |
| Shape_Volume_mL | 13.715     | 13.110                | 13.715         | 13.715              |
| NGLDM_Coarseness | 9.652        | 3.354                 | 5.714          | 4.278               |

Note.—Showing the top 10 selected features for all outcomes. GLCM = gray-level co-occurrence matrix, GLNU = gray-level nonuniformity, GLRLM = gray-level run length matrix, GLZLM = gray-level zone length matrix, LGRE = low gray-level run emphasis, LRE = long-run emphasis, LRLGE = long-run low gray-level emphasis, LZHGE = long-zone high gray-level emphasis, NGLDM = neighborhood gray-level different matrix, RLNU = run length nonuniformity, RP = run percentage, SD = standard deviation, SRLGE = short-run low gray-level emphasis, SZE = short-zone emphasis, SZHGE = short-zone high gray-level emphasis.

Kaplan-Meier Survival Analyses by the Random Forest Model of Texture Features

Kaplan-Meier survival analyses by the random forest model from ADC maps for predicting RFS using the cutoff value obtained by the ROC analysis were then generated for each of the parameters assessed (Table 6, Fig 4a–e). The random forest model for predicting high-grade cervical carcinomas showed that the mean RFS for high-grade cervical carcinomas was significantly shorter than that for low-grade cervical carcinomas (1230 days ± 164 vs 2108 days ± 162; P < .0001), with a hazard ratio of 2.7. The random forest model for predicting parametrial invasion also showed that the mean RFS for parametrial invasion was significantly shorter than that for its absence (826 days ± 204 vs 2116 days ± 137; P < .0001), with a hazard ratio of 10.6. The random forest model for predicting lymph node metastasis showed that the mean RFS was significantly shorter for the presence of, rather than for the absence of, lymph node metastasis (1507 days ± 179 vs 2108 days ± 127; P = .0344), with a hazard ratio of 3.0. The random forest model for predicting recurrence showed that the mean RFS was significantly shorter for presence of, than for absence of, recurrence (1006 days ± 195 vs 2091 days ± 150; P = .0015), with a hazard ratio of 5.2. Finally, ADC values for predicting recurrence showed that the mean RFS was significantly shorter for an ADC ≤ 0.779 × 10⁻³ mm²/sec than for an ADC > 0.779 × 10⁻³ mm²/sec (867 days ± 214 vs 1987 days ± 144; P = .0018), with a hazard ratio of 6.3 (Table 6, Fig 4f). We used adjusted hazard ratios for the analysis.

These results demonstrate that the ADC map random forest models and the ADC values could help predict RFS and, furthermore, that the random forest models for parametrial invasion and stages III–IV could be more useful indicators than ADC values for predicting RFS and for risk stratification in patients.
with cervical carcinoma.

Discussion

In this study, we aimed to determine if texture analysis of ADC maps could predict prognostic characteristics of cervical carcinoma. Our data showed that the random forest model from ADC maps allowed significantly higher diagnostic performance for discriminating high-grade from low-grade cervical carcinomas than did ADC values. Although there were no significant differences in ADC values between grade 2 and grade 3 cervical carcinomas, the random forest model showed significant differences between grade 2 and grade 3 cervical carcinomas. Because the histologic grade of cervical carcinoma is one of the strongest prognostic factors for local, regional lymph nodal, and distant recurrence, it has been widely used to stratify the risk of patients with carcinoma and help select and plan optimal treatment (2–6); however, noninvasive evaluation of the histologic grade of cervical carcinoma remains challenging (7–10). Given that the random forest model from ADC maps has significantly higher diagnostic performance for noninvasively evaluating the histologic grade of cervical carcinoma than ADC values, it may be a promising noninvasive tool for preoperative risk stratification and optimal selection of those high-risk patients who require more extensive treatment while preventing overtreatment of low-risk patients. Although the findings of a previous study (15) showed that texture analysis of ADC maps was associated with tumor differentiation, the study did not examine the correlation between the ADC map random forest model and the histologic grade of cervical carcinoma for predicting RFS. The results of this study, however, do show this type of correlation.

In addition, our results revealed that the random forest model from ADC maps had higher (although not significantly higher) diagnostic performance than that of ADC values for assessing parametrial invasion, lymph node metastasis, stages III–IV, and recurrence in patients with cervical carcinoma. Therefore, the higher diagnostic performance of the random forest model from ADC maps supports using the random forest model as a noninvasive method for predicting important prognostic factors, including parametrial invasion, lymph node metastasis, FIGO stage, and recurrence in patients with cervical carcinoma.

Furthermore, our data demonstrated that the random forest model from ADC maps could be useful for predicting RFS in patients with cervical carcinoma. The random forest model showed that the mean RFS rates were significantly shorter for high-grade cervical carcinomas than for low-grade cervical carcinomas ($P = .0405$, hazard ratio = 10.6), for presence of lymph node metastasis than for its absence ($P = .0344$, hazard ratio = 3.0), for stages III–IV than for stages I–II ($P = .0001$, hazard ratio = 9.9), and for presence of recurrence than for its absence ($P = .0015$, hazard ratio = 5.2). In addition, the mean RFS was significantly shorter for ADC $\leq 0.779 \times 10^{-3}$ mm$^2$/sec than for ADC $> 0.779 \times 10^{-3}$.

![Box plots of random forest model for different histologic grades of cervical carcinomas and for low-grade and high-grade cervical carcinomas.](image)
mm²/sec (P = .0018, hazard ratio = 6.3). Thus, some random forest models from ADC maps seem to reflect the aggressiveness of cervical carcinoma more accurately than ADC values (29,30). Given that predicting RFS is the final outcome in treating patients with cervical carcinoma, our results show that the random forest model from ADC maps can be an alternative for noninvasively predicting RFS in patients with cervical carcinoma. Recent studies have shown a correlation between ADC and the Ki-67 proliferation index in other tumors, which suggests an association between tumor cellularity and proliferation activity (31–33). Previous studies have reported that the texture features of various MR images were associated with prognosis (16–18), but they did not examine the correlation between the ADC map random forest model and histologic grade for predicting RFS. To the best of our knowledge, our study appears to be the first to show this correlation.

There were some limitations to our study. First, our study was a single-center retrospective one including a small sample size (58 patients) and histologic subtype (squamous cell carcinoma in 47 [81.0%] patients, adenocarcinoma in eight [13.8%] patients, and small cell carcinoma in three [5.2%] patients); thus, it may be premature to draw the conclusions for the prognostic performance of the reported texture features. Nevertheless, we were able to build random forest models for noninvasively evaluating histologic grade and other prognostic factors and for predicting RFS in patients with cervical carcinoma that had significantly higher diagnostic performance than ADC values. We believe that these findings require a study with a larger sample size as well as an external validation to confirm the prognostic performance of the reported textures features. Second, the ROIs were drawn by two observers in consensus, not independently. Ideally, the observers should perform separate segmentations and then determine the intra- and interobserver agreement, because it is well known that minor differences in segmentation have large effects on the texture analysis results. Third, there may be biased results in this study because the variables remain numerous on a small population, although several variables were removed for each of the five outcomes from 45 features analyzed. Therefore, further studies involving larger sample sizes are required to address these concerns. Fourth, this study was from a single institution using the same MRI scanner and the same software. Therefore, whether the random forest model can be applied to different MRI scanners and software remains to be validated. Last, while we were unable to provide technical details of the LIFEx software due to proprietary restraints, this program is freely available for other researchers to use on their own datasets to reproduce the results from this study by following our methods.
In conclusion, the random forest model from ADC maps improved diagnostic performance for assessing high-grade cervical carcinomas, parametrial invasion, lymph node metastasis, stages III–IV, and recurrence relative to the performance of using ADC values. The ADC map random forest models and ADC values were useful for predicting RFS, and the random forest models for parametrial invasion and stages III–IV were more useful than ADC values for predicting RFS and for risk stratification in patients with cervical carcinoma. Therefore, our findings suggest that texture analysis of ADC maps could be used for pretreatment prognostication and optimal treatment selection in patients with cervical carcinoma in the future. Further validation of texture analysis on ADC maps on

| Tumor grade Model and ADC Value | Mean RFS (d)   | Hazard Ratio | P Value |
|--------------------------------|---------------|--------------|---------|
| High grade                    | 1230 ± 164 (910, 1551) | 2.7 (1.0, 7.3) | .0405   |
| Low grade                     | 2108 ± 162 (1791, 2425) |             |         |

| Parametrial invasion           |               |             |         |
| Presence                       | 826 ± 204 (426, 1226) | 10.6 (3.5, <.0001) |         |
| Absence                        | 2116 ± 137 (1848, 2384) |            |         |

| Lymph node metastasis          |               |             |         |
| Presence                       | 1507 ± 179 (1156, 1859) | 3.0 (1.0, 8.9) | .0344   |
| Absence                        | 2108 ± 127 (1858, 2357) |             |         |

| Stage                          |               |             |         |
| III–IV                         | 737 ± 200 (346, 1128) | 9.9 (3.1, 32.2) | .0001   |
| I–II                           | 2024 ± 144 (1741, 2307) |             |         |

| Recurrence                     |               |             |         |
| Presence                       | 1006 ± 195 (625, 1388) | 5.2 (1.9, 14.3) | .0015   |
| Absence                        | 2091 ± 150 (1798, 2384) |             |         |

| ADC value (× 10^{-3} mm^2/sec) |         |             |         |
| ≤ 0.779                        | 867 ± 214 (448, 1286) | 6.3 (2.0, 20.2) | .0018   |
| > 0.779                        | 1987 ± 144 (1704, 2270) |             |         |

Note.—Data are mean values ± standard errors of the mean and data in parentheses are 95% confidence intervals. P value represents differences in comparison of survival curves (log-rank test). We used adjusted hazard ratios for the analysis. ADC = apparent diffusion coefficient, RFS = recurrence-free survival.

Figure 4: Kaplan-Meier survival analyses by the random forest model of texture features and the apparent diffusion coefficient (ADC) values for predicting recurrence-free survival (RFS) in patients with cervical carcinoma. Kaplan-Meier survival analyses by the random forest model for predicting (a) high-grade cervical carcinomas, (b) parametrial invasion, (c) lymph node metastasis, (d) stages III–IV, and (e) recurrence. (f) Kaplan-Meier survival analyses by ADC values for predicting recurrence. Random forest models, factors, mean RFS, hazard ratio, and P values are shown in Table 6. Thin curves indicate 95% confidence interval bands. RF = random forest, CC = cervical carcinoma. * = significantly different (P < .05).
larger populations of patients with cervical carcinoma will be needed to translate these findings for clinical use.

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