**MRI Texture Features Differentiate Clinicopathological Characteristics of Cervical Carcinoma**


## Abstract

*Objectives*

To evaluate MRI texture analysis in differentiating clinicopathological characteristics of cervical carcinoma (CC).

*Methods*

Patients with newly diagnosed CC who underwent pre-treatment MRI were retrospectively reviewed. Texture analysis was performed using commercial software (TexRAD). Largest single-slice ROIs were manually drawn around the tumours on T2-weighted (T2W) images, ADC maps and contrast-enhanced T1-weighted (T1c) images. First-order texture features were calculated and compared among histological subtypes, tumour grades, FIGO stages and nodal status by Mann-Whitney U test. Feature selection was achieved by elastic net. Selected features from different sequences were used to build the multivariable support vector machine (SVM) models and the performances were assessed by ROC curves and AUC.

*Results*

Ninety-five patients with FIGO stage IB~IVB were evaluated. A number of texture features from multiple sequences were significantly different among all the clinicopathological subgroups ($p < 0.05$). Texture features from different sequences were selected to build the SVM models. The AUCs of SVM models for discriminating histological subtypes, tumour grades, FIGO stages and nodal status were 0.841, 0.850, 0.898 and 0.879, respectively.

*Conclusions*

Texture features derived from multiple sequences were helpful in differentiating the clinicopathological signatures of CC. The SVM models with selected features from different sequences offered excellent diagnostic discrimination of the tumour characteristics in CC.

*Key points*

- *First-order texture features are able to differentiate clinicopathological signatures of cervical carcinoma.*
- *Combined texture features from different sequences can offer excellent diagnostic discrimination of the tumour characteristics in cervical carcinoma.*

**Keywords**

Magnetic resonance imaging; Squamous cell carcinoma; Adenocarcinoma; Area under curve; Entropy

**Abbreviations**

ACA adenocarcinoma
ADC apparent diffusion coefficient
AUC area under the curve
CC cervical carcinoma
DWI diffusion-weighted imaging
MPP mean of positive pixels
MRI magnetic resonance imaging
ROI region of interest
SCC squamous cell carcinoma
SD standard deviation
SSF spatial scale filters
SVM support vector machine
T1c contrast-enhanced T1-weighted
T2W T2-weighted
VOI volume of interest

## 1. Introduction

Magnetic resonance imaging (MRI) is used in the local staging of cervical carcinoma (CC). T2-weighted (T2W) imaging provides important information on the tumour morphology and detailed assessment of the local disease extent in the pelvis. Diffusion-weighted imaging (DWI) provides information of cellular architecture, allowing both qualitative and quantitative analyses of tumour cellularity in cancers

[1]. Apparent diffusion coefficient (ADC) generated from conventional DWI can reflect tissue physiological features and tumour microstructure. Contrast-enhanced T1-weighted (T1c) imaging is able to evaluate the tumours' vascularity and enhancement. In CC, ADC could aid in histological subtyping and tumour grading [2-6]. It has also been previously shown that T1c imaging yielded better definition of tumour to assist localization and improved contrast-to-noise ratio compared to T2-weighted (T2W) images, especially in small tumour [7].

Tumour heterogeneity is a crucial determinant in predicting tumour aggressiveness and can be reflected on oncological images. Texture analysis allows the evaluation of grey-level intensity and the positions of pixels on images by using mathematical approaches. A range of texture features are generated for the measurement of intra-tumour complexity and heterogeneity [8, 9]. Texture analysis is emerging as an important and promising imaging tool for quantifying tumour heterogeneity, which could not be readily appreciated by radiologists' naked eyes.

Visual assessment of the appearance of CC on MRI could be similar, in spite of the diverse histological subtypes and clinical behaviours [8]. Several studies have reported the value of MRI texture analysis in CC, mostly on cancer prognosis, while few literature explored the abilities of texture features in the clinicopathological characterization of CC [9-14]. The purpose of this study was to evaluate the value of texture analysis derived from T2W images, ADC maps and T1c images in the characterization of CC, specifically in differentiating histological subtypes, tumour grades, FIGO stages and nodal status.

## 2. Materials and methods

### 2.1 Patients

This retrospective study was approved by the local Institutional Review Board and in accordance with the Helsinki Declaration. Informed consent was waived. Inclusion criteria included (a) histological confirmed CC, (b) without prior history of surgery, chemoradiation or other malignancy, (c) T2W imaging, DWI and T1c imaging were all performed. Exclusion criteria were those with (a) contraindications to exogenous MRI contrast agent, (b) maximum tumour volume smaller than 1.5cm$^3$, (c) incomplete

clinicopathological data, (d) rare histological subtypes. For the threshold of minimum tumour volume, it was chosen to allow accurate tumour delineation and reduce partial volume effect.

Cervical biopsies were reviewed by experienced pathologist specialized in gynaecological malignancy and discussed at multi-disciplinary team (MDT) meetings. The assessed pathological markers included histological subtypes and tumour grades according to the WHO Classification of Tumours of Female Reproductive Organs [15]. Histological subtypes were separated into two subgroups: squamous cell carcinoma (SCC) and adenocarcinoma (ACA). The other rarer subtypes were excluded. Tumour grades were dichotomised into well-moderately differentiated (G1~2) and poorly differentiated (G3).

All cases were restaged using the revised 2018/9 FIGO staging for CC by a board-certified radiologist (>10 years' experience in pelvic MRI) [16]. FIGO stages were dichotomised between low FIGO stages (I~II) and high FIGO stages (III~IV). Nodal status was based on MRI interpretation of T2W images, positive or involved lymph node was defined as enlarged lymph node with short axis larger than 10 mm, with lobulated or spiculated margin, or the presence of necrosis [17, 18].

### 2.2 Imaging acquisition

MRI examinations were performed on a 3.0T platform (Achieva 3T TX, Philips Healthcare) with a 16-channel phased array torso coil. All the patients fasted for 6 hours and received 20 mg intravenous hyoscine butylbromide (Buscopan, Boehringer Ingelheim) before MRI examinations to reduce the peristaltic artefacts. All recruited patients had T2W, DWI and T1c sequences acquired before surgery or chemoradiation. MRI sequences were standardized for all patients and the clinical protocol was designed in accordance to the guidelines of the European Society of Urogenital Radiology (Table 1) [19].

### 2.3 Texture features extraction

T2W images, ADC maps and T1c images were used for MRI texture features extraction. T2W and T1c images were normalised using *p*-normalisation. ADC maps

were generated using vendor software provided on the ViewForum workstation (Philips Healthcare) with 2 *b*-values (0 and 1000 s/mm$^2$). Texture analysis was performed with commercial software TexRAD (Feedback Medical Ltd).

First, a radiologist (board-certified with 3 years' experience in pelvic MRI) delineated the region-of-interest (ROI) on the largest single-slice of CC on T2W image, ADC map and T1c image for each patient. A free-hand polygonal ROI was drawn around the tumour by strictly delineating its border from adjacent normal tissue (Figure 1). T2W images were taken as reference when drawing ROIs on ADC maps and T1c images. The ROIs from the same patient on different sequences were kept consistent on the same anatomical slice. Subsequently, the ROIs were verified by a senior board-certified radiologist (>10 years' experience in pelvic MRI). Both radiologists were blinded to the clinicopathological results.

Six texture features were extracted from the first-order statistics with 6 spatial scale filters (SSF) using TexRAD, including mean (average grey-level intensity values), standard deviation (SD; degree of variation of pixel values), entropy (irregularity of grey-level distribution), mean of positive pixels (MPP; pixel with values greater than 0), skewness (asymmetry of the histogram), and kurtosis (peakedness of the histogram) [20]. The SSF was the filtration step in reducing the effects of photon noise in the quantification of texture analysis. This step highlighted texture features at different anatomical spatial scales ranging from fine to coarse texture. The 6 sizes of SSF were 0 (without filtration), 2 mm (fine texture scale), 3~5 mm (medium texture scale) and 6 mm (coarse texture scale) (Figure 1). Thus, a total of 108 texture features from T2W images, ADC maps and T1c images were extracted from each patient and compared among histological subtypes, tumour grades, FIGO stages and nodal status.

**2.3 Statistical analysis**

All statistical analyses were performed on RStudio (v1.2.5033, RStudio, lnc.). Data was tested for normality and some texture features were not normally distributed, hence Mann-Whitey U tests were used to compare the texture features in different dichotomised clinicopathological groups (histological subtypes, tumour grades, FIGO stages and nodal status). A two-tailed $p$-value < 0.05 was considered statistically

significant.

Prediction models based on support vector machine (SVM) models using texture features to predict the clinicopathological subgroups were also developed. Elastic net regularisation was first used to select texture features that were shown to be statistically significant between clinicopathological subgroups [21]. It has been shown that using Mann-Whitney U test as one of the criteria for feature selection produced robust models [22]. Goodness-of-fit metrics were then used to select the best parsimonious models. To build the SVM models, 80% of the cohort was designated as the training set and the remaining 20% of the cohort was designated as the validation set. A radial kernel was used, and the validation sets were used to tune the hyperparameters (cost and gamma). The receiver operating characteristic (ROC) curves and areas under the curve (AUC) were then calculated to measure the predictive performances of each model. AUC > 0.8 was considered as an excellent accuracy [23].

## 3. Results

### 3.1 Clinical characteristics

From March 2013 to February 2019, 95 patients were recruited in this study. The demographics and clinical characteristics of the patients are displayed in Table 2.

### 3.2 Univariable analysis in the characterisation of CC

#### 3.2.1 Histological subtypes

On T2W images, Mean2~6, MPP2~6 and Skewness2~3 were all significantly lower in SCC than ACA. On ADC maps, SD0, MPP2~6, Entropy0 and Skewness3~4 were lower in SCC than ACA, while Kurtosis0 was higher in SCC than ACA. As for T1c images, only Mean0 and MPP0 were higher in SCC (Table 3).

#### 3.2.2 Tumour grades

No significant differences in texture features on T2W images were observed. On ADC maps, Mean2~4, Skewness0, Kurtosis0 and Kurtosis4 were significantly higher in well-moderately differentiated (G1~2) compared to poorly differentiated (G3) tumour

grades. On T1c images, Skewness4 was higher in G1~2 (Table 3).

### 3.2.3 FIGO stages

For T2W, SD2, MPP2~5 and Entropy2 significantly decreased from low FIGO stages (FIGO I~II) to high FIGO stages (FIGO III~IV), whereas Skewness0 and Kurtosis3 were increased. However, for ADC, Mean2~6 and Entropy0~6 increased from FIGO I~II to FIGO III~IV. On T1c, Entropy5~6 and Skewness4~5 significantly increased from FIGO I~II to FIGO III~IV (Table 3).

### 3.2.4 Nodal status

For T2W, Skewness0 and Kurtosis3~4 were observed to be significantly higher in positive nodal status as compared with negative nodal status. For ADC, Mean3~6 and Entropy0~6 were significantly higher in positive nodal status as compared with negative nodal status. As with T1c, Entropy5~6 were higher in positive nodal status than those without lymph node involvement (Table 3).

## 3.3 Multivariable analysis in the characterisation of CC

Multivariable SVM models of discriminating these 4 dichotomized characteristics were built with selected texture features. The selected features and respective AUC, accuracy, sensitivity and specificity of these 4 SVM models are summarized in Table 4.

## 4. Discussion

In our study, a number of texture features at multiple SSFs demonstrated significant differences among histological subtypes, tumour grades, FIGO stages and nodal status. By applying SVM models using selected texture features from different sequences, all the 4 models generated excellent performances in the diagnostic differentiation.

The commercial software used in this study offers first-order statistics that describe global texture features according to the grey-level frequency distribution within the tumour. There are other texture analyses that include second-order and high-order statistics, which reflect local texture features and regional intensity variations [24]. To

date, several studies reported second-order features of MRI had potential ability in predicting clinical recurrence or outcome of CC, especially the excellent performance of entropy in ADC [9, 25, 26]. However, there is limited literature that focused on the value of texture analysis in determining different clinicopathological features of CC [10, 14]. In other pelvic and abdominal cancers, first-order texture analysis was able to differentiate tumour invasive features, subtypes or grades [27-30]. Additionally, the repeatability of MRI global first-order texture features was superior to that of local-regional second-order and high-order statistics, suggesting that first-order texture analysis would offer robust use in clinical practice [31].

In the present study, we found that SCC had lower MPP than ACA on both T2W and ADC. Similarly, mean on T2W was also lower in SCC. Our findings were concordant with a recent study that showed the mean of T2W in SCC was lower than ACA. These findings were thought to be due to tightly packed cells and restricted extracellular space in SCC, which could contribute to more positive pixels when SSFs are applied. In contrast, ACA contains solid and fluid compositions that would result in more heterogeneous distribution of pixels, both positive and negative pixels [10]. It was shown that ADC-derived mean and MPP were positively correlated with ADC value, and this was in line with previous study that ADC of SCC was lower than ACA [29, 32]. In endometrial carcinoma, high MPP in T1c images could independently predict high-risk histological subtype [28]. Besides, T2W_Skewness2~3 were also lower in SCC, which was in line with Ciolina *et al*., SCC presented lower mean and skewness derived from T2W imaging in comparison with ACA [10]. Whereas, Goyal *et al*. reported many texture features (mean, SD, entropy and skewness) were able to distinguish clear cell renal carcinoma from non-clear cell carcinoma, but MPP was not different between subtypes [30]. The discrepancy could be related to the different organs under investigation and therefore, results from texture analysis are likely organ- and disease-specific.

ADC_Mean2~4 were lower in G3 compared to G1~2 tumours. This is in agreement with previous studies that showed lower ADC values in high-grade CC [2-5]. Fewer features were significant among tumour grades compared to other clinicopathologic factors, and none observed on T2W images. This is likely related to the lack of unified

histological criteria for CC grading, making it largely subjective and may not be an accurate histological marker to compare with T2W texture features [33]. It was also found that there is high inter-observer and intra-observer variability in tumour grading which contributes to the inconsistency of tumour grading in CC [34]. As the cohort recruited in our study was mostly locally advanced CC who underwent chemoradiation, surgical pathological assessment could not be performed and tumour grading was based on biopsy samples, which could make the grading process more challenging when working with little tissue specimens.

Higher mean and entropy at multiple SSFs derived from ADC were found in high FIGO stages (FIGO III~IV), and those with nodal metastases. For mean, it could be explained by the lower ADC values observed in advanced tumours [32]. As for entropy, it corroborated with results from previous studies in CC and endometrial carcinoma [12, 28]. Furthermore, ADC-derived entropy at multiple SSFs had higher feature importance in the random forest model generated to detect deep myometrial invasion or lymphovascular space invasion in endometrial carcinoma [27]. T1c_Entropy5~6 were higher in FIGO III~IV and positive nodal status. It was hypothesised that features with fine textures scale (SSF = 2) might not reflect biologically important features because the textures at that spatial scale were more susceptible to variation in image acquisition parameters [29]. We proposed that entropy at a coarse scale (SSF = 6) on T1c would enhance the appreciation of the underlying heterogeneity in tumour vasculature and perfusion. Entropy represents the irregularity of grey-level distribution, therefore higher heterogeneity was associated with advanced stage CC [35]. Furthermore, entropy was also associated with tumour expression, metabolism, prognosis and treatment response [36]. Accordingly, it has become a promising quantitative imaging biomarker for the characterization of cancer phenotype. Lastly, T2W_MPP2~5 were lower in FIGO III~IV compared to FIGO I~II, which could be related to microscopic tumour hypoxia and necrosis that contributed to increase number of low signal pixels on T2W images [37].

Skewness derived from multiple sequences was also a significant feature in different clinicopathological subgroups. T2W_Skewness2~3, ADC_Skewness3~4 were lower in SCC than ACA, which were consistent with previous findings in locally advanced

cervical cancer [10]. Higher T1c_Skewness4~5 were observed in FIGO III~IV compared to FIGO I~II. Skewness reflects the asymmetry of pixel distribution. Predominantly positive pixels would result in more positive skewness, and predominantly negative pixels result in negative skewness [20]. Advanced tumours have more heterogeneous enhancement with intratumoural spatial variation, including well enhanced viable tumour and non-enhancing necrotic core, which could result in a wider and more asymmetric distribution of pixels' intensities on T1c [8].

As the same features at different SSFs were highly correlated, elastic net was used for further feature selection. The combined selected texture features from different sequences in the SVM models demonstrated excellent discriminatory capability with balanced sensitivities and specificities, especially in dichotomising FIGO stages (AUC = 0.898). Multi-parametric MRI is used in radiomic studies of various tumours [38, 39]. The diagnostic performances of the models generated in this study signified the complementary roles of different sequences in the tumour characterisation of CC. In early-stage CC, SVM models using both T2W imaging and ADC could distinguished pelvic lymph node metastasis and parametrial invasion (AUC = 0.893 and 0.946, respectively) [40, 41]. It also consolidated the notion of combining texture features from different sequences in identification of aggressive tumour characteristics. Among the selected features of our SVM models, FIGO stages and nodal status shared 2 common features, T2W_Skewness0 and ADC_Entropy3. This was likely due to the fact that 2018/2019 FIGO staging is affected by the nodal status.

There are several limitations in our study. First, volumetric texture analysis was not available on TexRAD. Herein, all the texture analyses were based on the largest single-slice ROIs, which might not represent the global tumour heterogeneity. Nevertheless, other studies have shown that the use of single-slice analysis in texture analysis was clinically useful [27, 28, 42]. Second, the lymph node status was assessed by a radiologist using the size and morphology criteria and histological confirmation was not possible in majority of the patients in this cohort as these patients underwent definitive chemoradiation instead of surgery. This could limit the accuracy in distinguishing nodal status. Third, our limited sample size precluded the use of an independent test set for assessing predictive performance. Lastly, the

unbalanced distributed histological subtypes would suffer from selection bias; however, the ratio between SCC and ACA in this study was in keeping of the prevalence of histological subtypes distribution in CC.

In conclusion, texture features derived from multiple sequences showed potential ability in differentiating clinicopathological signatures of CC. The multivariable SVM models with combined selected texture features from different sequences provided excellent diagnostic accuracies in discriminating characteristics in CC.

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Table 1. MRI protocols

| Sequences | T2W TSE | T2W TSE SPAIR | T2W TSE | T2W TSE | DWI | CE 3D T1W THRIVE |
|---|---|---|---|---|---|---|
| Plane | Sagittal | Coronal | Axial | Oblique Axial | Axial | 3D |
| TR/TE (ms) | 4000/80 | 3500/80 | 2800/100 | 2800/100 | 2000/54 | 3/1.4 |
| Turbo factor | 30 | 21 | 12 | 14 | NA | NA |
| FOV (mm) | 240×240 | 230×230 | 402×300 | 220×220 | 406×300 | 370×203 |
| Matrix size | 480×298 | 352×300 | 787×600 | 316×311 | 168×124 | 248×134 |
| Slice thickness (mm) | 4 | 4 | 4 | 4 | 4 | 1.5 |
| Intersection gap (mm) | 0 | 0 | 0 | 0 | 0 | 0 |
| Bandwidth (Hz/pixel) | 230 | 186 | 169 | 162 | 15.3 | 724 |
| Number of excitations | 2 | 1 | 1 | 1 | 2 | 1 |

T2W: T2-weighted; TSE: turbo spin echo; SPAIR: spectral attenuated inversion recovery; DWI: diffusion-weighted imaging; CE: contrast enhanced; T1W: T1-weighted; THRIVE: T1 high-resolution isotropic volume excitation; TR/TE: repetition time / echo time; FOV: field of view.

Table 2. Clinical characteristics

| Characteristics | Patients (n) |
|---|---|
| **Number** | 95 |
| **Age (years)** | 55.4 ± 13.5 (range 21~93) |
| **Histological subtype** | |
| **Squamous cell carcinoma (SCC)** | 77 |
| **Adenocarcinoma (ACA)** | 18 |
| **Tumor grade** | |
| **G1** | 5 |
| **G2** | 35 |
| **G3** | 55 |
| **FIGO stage** | |
| **I** | 8 |
| **II** | 33 |
| **III** | 51 |
| **IV** | 3 |
| **Nodal status** | |
| **Positive** | 48 |
| **Negative** | 47 |

Table 3. Significant texture features in histological subtypes, tumour grades, FIGO stages and nodal status

| Histological subtypes | | Tumour grades | | FIGO stages | | Nodal status | |
|---|---|---|---|---|---|---|---|
| Sequences/ Features | *p*-value | Sequences/ Features | *p*-value | Sequences/ Features | *p*-value | Sequences/ Features | *p*-value |
| **T2W** | | **T2W** | | **T2W** | | **T2W** | |
| Mean2 | 0.0029 | | | SD2 | 0.0347 | Skewness0 | 0.0436 |
| Mean3 | 0.0013 | | | MPP2 | 0.0237 | Kurtosis3 | 0.0295 |
| Mean4 | 0.0008 | | | MPP3 | 0.0226 | Kurtosis4 | 0.0345 |
| Mean5 | 0.0014 | | | MPP4 | 0.0160 | | |
| Mean6 | 0.0020 | | | MPP5 | 0.0221 | | |
| MPP2 | 0.0322 | | | Entropy2 | 0.0215 | | |
| MPP3 | 0.0208 | | | Skewness0 | 0.0338 | | |
| MPP4 | 0.0139 | | | Kurtosis3 | 0.0325 | | |
| MPP5 | 0.0123 | | | | | | |
| MPP6 | 0.0161 | | | | | | |
| Skewness2 | 0.0004 | | | | | | |
| Skewness3 | 0.0099 | | | | | | |
| **ADC** | | **ADC** | | **ADC** | | **ADC** | |
| SD0 | 0.0165 | Mean2 | 0.0170 | Mean2 | 0.0072 | Mean3 | 0.0406 |
| MPP2 | 0.0363 | Mean3 | 0.0127 | Mean3 | 0.0058 | Mean4 | 0.0461 |
| MPP3 | 0.0188 | Mean4 | 0.0291 | Mean4 | 0.0083 | Mean5 | 0.0429 |
| MPP4 | 0.0315 | Skewness0 | 0.0119 | Mean5 | 0.0077 | Mean6 | 0.0478 |
| MPP5 | 0.0071 | Kurtosis0 | 0.0355 | Mean6 | 0.0088 | Entropy0 | 0.0046 |
| MPP6 | 0.0055 | Kurtosis4 | 0.0487 | Entropy0 | 0.0012 | Entropy2 | 0.0022 |
| Entropy0 | 0.0279 | | | Entropy2 | 0.0002 | Entropy3 | 0.0020 |
| Skewness3 | 0.0358 | | | Entropy3 | 0.0001 | Entropy4 | 0.0022 |
| Skewness4 | 0.0416 | | | Entropy4 | 0.0001 | Entropy5 | 0.0032 |
| Kurtosis0 | 0.0197 | | | Entropy5 | 0.0002 | Entropy6 | 0.0025 |
| | | | | Entropy6 | 0.0001 | | |
| **T1c** | | **T1c** | | **T1c** | | **T1c** | |
| Mean0 | 0.0354 | Skewness4 | 0.0399 | Entropy5 | 0.0490 | Entropy5 | 0.0498 |
| MPP0 | 0.0354 | | | Entropy6 | 0.0302 | Entropy6 | 0.0371 |
| | | | | Skewness4 | 0.0174 | | |
| | | | | Skewness5 | 0.0477 | | |

Table 4. Summary of the SVM models

| SVM models | Selected features | AUC | Accuracy | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Histological subtypes** | T2W_Skewness2<br>ADC_MPP5 | 0.841 | 0.853 | 0.857 | 0.833 |
| **Tumour grades** | ADC_Mean3<br>ADC_Skewness0<br>T1c_Skewness4 | 0.850 | 0.842 | 0.873 | 0.800 |
| **FIGO stages** | T2W_Skewness0<br>ADC_Entropy3<br>T1c_Skewness4 | 0.898 | 0.853 | 0.870 | 0.829 |
| **Nodal status** | T2W_Skewness0<br>ADC_Entropy3<br>T1c_Entropy5 | 0.879 | 0.821 | 0.812 | 0.830 |

Figure 1. A 28-year-old patient with squamous cell carcinomas (SCC), G3 and FIGO IIIC1. ROI delineation on T2W image, ADC map and T1c image, with corresponding texture images at SSF = 2, 4 and 6, respectively.