Prognostic value of textural features obtained from F-fluorodeoxyglucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) in patients with locally advanced cervical cancer undergoing concurrent chemoradiotherapy

Hyun-Woong Cho1 · Eun Seong Lee2 · Jae Kwan Lee1 · Jae Seon Eo2 · Sungeun Kim3 · Jin Hwa Hong1

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Abstract

Objective To evaluate whether textural features obtained from F-18 FDG PET/CT offer clinical value that can predict the outcome of patients with locally advanced cervical cancer (LACC) receiving concurrent chemoradiotherapy (CCRT).

Methods We reviewed the records of 68 patients with stage IIB–IVA LACC who underwent PET/CT before CCRT. Conventional metabolic parameters, shape indices, and textural features of the primary tumor were measured on PET/CT. A Cox regression model was used to examine the effects of variables on overall survival (OS) and progression-free survival (PFS).

Results The patients included in this study were classified into two groups based on median value of PET/CT parameters. The high group of GLNU derived from GLRLM is only independent prognostic factor for PFS (HR 7.142; 95% CI 1.656–30.802; \( p = 0.008 \)) and OS (HR 9.780; 95% CI 1.222–78.286; \( p = 0.031 \)). In addition, GLNU derived from GLRLM (AUC 0.846, 95% CI 0.738–0.923) was the best predictor for recurrence among clinical prognostic factors and PET/CT parameters.

Conclusion Our results demonstrated that high GLNU from GLRLM on pretreatment F-18 FDG PET/CT images, were significant prognostic factors for recurrence and death in patients with LACC receiving CCRT.

Keywords Textural features · Prediction · Cervical cancer · Chemoradiotherapy

Introduction

Cervical cancer is one of the most common cancers among women with over 500,000 new cases annually worldwide, resulting in over 270,000 deaths [1]. A significant proportion of patients are diagnosed at a locally advanced stage [2]. Concurrent chemoradiotherapy (CCRT) became standard care for women with locally advanced cervical cancer (LACC) following a National Cancer Institute (NCI) alert based on the results of 5 randomized trials in 1999 [3–8]. However, approximately 30–40% of women with LACC are unable to achieve complete response after CCRT [9]. The International Federation of Gynecology and Obstetrics (FIGO) staging, histology, tumor size and lymph node (LN) metastases are known as prognostic factors, but even patients with the same clinical factors may have different clinical outcomes [10]. Therefore, novel markers to better identify patients at high risk of relapse are needed.

F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is essential in the initial evaluation of disease extent and in assessment of responses to CCRT in LACC [11]. Many studies have suggested that additional quantitative features available from PET/CT, such as standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis...
(TLG), could provide predictive or prognostic information [12–19]. A recent meta-analysis of 12 studies involving cervical cancer demonstrated that the prognostic values of MTV and TLG for recurrence were consistently significant, with pooled hazard ratios (HRs) of 5.08–7.30 and 4.80–15.83, respectively [20]. However, these parameters do not reflect intratumor heterogeneity (ITH), which is one of the main causes of resistance to treatment [21, 22]. One of the most highlighted methods to quantify ITH is texture analysis from images [23]. Imaging analysis, including texture analysis, can be used to quantify tumor characteristics such as intensity, shape, and heterogeneity, some of which can provide clinically relevant and complementary information beyond conventional clinical characteristics in several cancers, including cervical cancer [24–29]. A number of recent studies have attempted textural analysis from PET/CT imaging to evaluate prognostic and predictive values after CCRT [10, 30, 31], but few studies have conducted a comprehensive analysis of clinical factors, conventional metabolic parameters, and textural features extracted from pretreatment PET/CT in LACC patients. Therefore, the purpose of this study is to evaluate whether the textural features obtained from F-18 FDG PET/CT imaging, based on comprehensive analysis, have clinical value that can predict the outcome of patients with LACC receiving CCRT.

Materials and methods

Patients

Patients with histologically proven LACC, staged IIB–IVA (FIGO 2009 definition) and treated with definitive curative CCRT and subsequent brachytherapy from January 2011 to November 2018 (to ensure a minimum follow-up of 1 year) at two institutions were included in this retrospective study. Enrollment required: (a) histologically confirmed stage IIB–IVA LACC determined by the 2018 FIGO classifications and (b) availability of follow-up information up to 24 months. Exclusion criteria were history of previous chemotherapy or radiotherapy and/or distant metastatic disease.

Pretreatment evaluation consisted of patient history evaluation and physical examination, gynecological evaluation with biopsy, complete blood analysis, urine analysis, chest radiography, sigmoidoscopy, pelvic magnetic resonance imaging (MRI), abdominopelvic CT, and F-18 FDG PET/CT. Cystoscopy was performed if necessary.

Medical records of patients including age and date of diagnosis, histology, 2018 FIGO stage, presence of positive LN on PET/CT which is determined by a nuclear radiologist, tumor size as measured on MRI, external beam radiotherapy (EBRT) and brachytherapy doses, and date and status (i.e., alive, deceased, and recurrence) at the last follow-up were retrieved. The date and site of recurrence were also collected.

Treatment

In patients scheduled for CCRT, a total of 54 Gy of external radiation (daily 2 Gy per fraction) was delivered. The radiation field was extended in patients with FDG uptake in the para-aortic lymph nodes. High-dose-rate brachytherapy was performed using 3.5 Gy per fraction, given in 8 fractions. Concurrent platinum-based chemotherapy was also administered to patients, and the chemotherapy regimens were as follows: weekly cisplatin (n = 41; 60.3%), paclitaxel-carboplatin (n = 19; 27.9%), and 5-FU-cisplatin (n = 8; 11.8%).

Follow-up

After completion of treatment, follow-up examinations consisting of cervical smear, pelvic MRI with or without abdominopelvic CT, and serum tumor marker analysis were performed every 3 months for 2 years and at 6-month intervals for 3 years thereafter. Recurrence was confirmed by imaging studies or biopsy.

PET/CT acquisition and image analysis

Pretreatment PET/CT images were acquired using combined PET/CT scanners [Gemini TF/16 channel PET/CT scanner (Philips Medical Systems, Cleveland, OH, USA)] for all patients at the two participating institutions following routine clinical PET/CT protocols. After fasting for at least 6 h, patients were given an intravenous injection of F-18 FDG; then, we waited approximately 60 min before scanning. A 1-min emission scan per bed position of PET scans was then, we waited approximately 60 min before scanning. A 1-min emission scan per bed position of PET scans was acquired immediately after unenhanced CT scan acquisition. The PET images were reconstructed to a 144 × 144 matrix size with a 4 mm slice thickness by means of an ordered subset expectation maximization algorithm incorporating time-of-flight information (3 iterations, 33 subsets).

LIFEx v.5.10 (https://www.lifexsoft.org) was used to delineate the volume of interest (VOI) of primary tumors and for extraction of each SUV metric and volumetric and radiomic feature [32]. The VOI on PET images was manually drawn with an SUV cutoff of 2.5 by a nuclear medicine physician who was blinded to patients’ clinical information. The following input parameters was used for calculation of features using LIFEx: 4.0 mm, 4.0 mm, 4.0 mm for spatial resampling; the number of gray levels in 64 bins for intensity discretization; absolute scale bounds between a minimum of 0 and a maximum of 25 for intensity rescaling.
PET/CT parameters

Conventional metabolic parameters [maximum SUV (SUVmax), MTV, and TLG], shape indices (sphericity, compacity, volume), histogram features (skewness, kurtosis, entropy, energy), and the four groups of textural features [gray level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), gray-level zone length matrix (GLZLM), and neighborhood gray-level different matrix (NGLDM)] retrieved from pre-treatment F-18 FDG PET/CT images were used in this study.

The SUVmax was defined as the maximum SUV within the tumor and the MTV was defined as tumor volume over 2.5 of SUV [33]. The TLG was calculated by multiplying the MTV with its corresponding mean SUV [34].

Sphericity is how sphere-shaped the VOI is. Sphericity is equal to 1 for a perfect sphere. Compacity reflects how compact the VOI is. Volume is the VOI in mL and in voxels.

GLCM takes into account the arrangements of pairs of voxels to calculate textural indices. The GLCM is calculated from 13 different directions in 3D with a δ-voxel distance (1d1) relationship between neighbouring voxels. The index value is the average of the index over the 13 directions in space (X, Y, Z). Seven textural indices are computed from this matrix.

NGLDM corresponds to the difference of gray levels between one voxel and its 26 neighbors in three dimensions (8 in 2D). Three texture indices can be computed from this matrix.

GLRLM gives the size of homogeneous runs for each gray level. This matrix is computed for the 13 different directions in 3D (4 in 2D) and for each of the 11 texture indices derived from this matrix, the 3D value is the average over the 13 directions in 3D (4 in 2D). The element (i, j) of GLRLM corresponds to the number of homogeneous runs of j voxels with intensity i in an image and is called GLRLM (i, j) thereafter.

GLZLM provides information on the size of homogeneous zones for each gray level in three dimensions (or 2D). It is also named Gray Level Size Zone Matrix (GLSZM). From this matrix, 11 texture indices are computed. Element (i, j) of GLZLM corresponds to the number of homogeneous zones of j voxels with the intensity i in an image and is called GLZLM (i, j) thereafter.

Skewness is the asymmetry of the gray-level distribution in the histogram. Kurtosis reflects the shape of the gray-level distribution (peaked or flat) relative to a normal distribution. Entropy reflects the randomness of the distribution. Energy reflects the uniformity of the distribution.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as “median (range)”. We used the Mann–Whitney U test for analysis of continuous variables, and Chi-squared test or Fisher’s exact test for analysis of categorical variables. To examine correlations between PET/CT parameters and disease recurrence, receiver operating characteristic (ROC) curves were constructed to evaluate the optimal predictive performance among the various textural indices, conventional PET/CT parameters, and clinical parameters, such as stage, node metastasis, and tumor size.

We split the patients (median) into two groups (high/low) per PET-CT parameters. For the high and low groups, survival curves were estimated according to the Kaplan–Meier method. Survival estimates were compared between the groups using the log-rank test. Univariate Cox proportional hazards regression models were used to identify significant prognostic factors for progression-free survival (PFS) and overall survival (OS). For feature reduction before multivariate analysis, PET parameters with significance (p < 0.05) from the univariate Cox regression were compared with each other by Pearson correlation. The parameter with more significant p value from the univariate Cox regression was selected first, and the parameters with a low correlation (p > 0.05 or −0.5 < r value < 0.5) to this were sequentially selected. MTV, TLG were additionally selected although highly correlated, based on the prior knowledge [35]. We also applied false discovery rate (FDR) correction to the q-value (FDR adjusted p value, cutoff < 0.05) to assess the significance of the features [36].

OS time was calculated from treatment initiation to all deaths (cancer-related or not). PFS time was calculated from treatment initiation and tumor progression, or death from any cause. Associations are shown as HRs with 95% confidence intervals (CIs), and values of p < 0.05 were considered statistically significant. All analyses were performed using the SAS statistical package (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and treatment outcomes

The clinical characteristics of study participants are listed in Table 1. The median age was 60 (27–75) years. The predominant FIGO stage was IIIC. After a median follow-up of 49 (12–139) months, disease recurrence occurred in 22 patients (32.3%), and 5 patients (7.4%) died. Of the 22 patients who underwent disease recurrence, 17 had a local recurrence and 5 had a distant recurrence. There were no differences in age, parity, histology, and chemotherapy.
regimen in patients with and without recurrence. However, IIIC and IVA staging were more common in patients with recurrence compared with those who did not experience recurrence ($p = 0.01$).

**Representative cases**

Two representative cases of the same cervical cancer stage with similar TLG have been shown in Fig. 1. Figure 1a shows F-18 FDG PET/CT images of cervical cancer patients with relatively high SUVmax, and relatively low textural values. On the other hand, Fig. 1b presents F-18 PET/CT images of a 42-year-old woman with stage IIB cervical squamous cell carcinoma. Trans-axial PET/CT and PET imaging revealed a mass lesion (red arrow) with relatively similar metabolic value (SUVmax, 8.4; TLG, 329.7), but relatively higher heterogeneity value (shape descriptor compacity, 2.33; GLNU from GLRLM, 94.4). The patient had disease recurrence 7 months after CCRT and subsequently died.

| Table 1 Clinical characteristics in patients with or without recurrence | All ($n=68$) (%) | No recurrence ($n=46$) (%) | Recurrence ($n=22$) (%) | $p$ value |
|---|---|---|---|---|
| Median age, year (range) | 60 (27–75) | 59 (34–78) | 59 (27–75) | 0.38 |
| Median parity (range) | 2 (0–7) | 2 (0–4) | 2 (0–3) | 0.63 |
| FIGO stage | | | | |
| IIB | 25 (36.8) | 22 (47.8) | 3 (13.6) | 0.01 |
| IIIC | 31 (45.6) | 19 (41.3) | 12 (54.5) |  |
| IVA | 12 (17.6) | 5 (10.9) | 7 (31.8) |  |
| Histology | | | | |
| Squamous cell carcinoma | 61 (89.7) | 41 (89.1) | 20 (90.9) | 0.55 |
| Adenocarcinoma | 4 (5.9) | 2 (4.3) | 2 (9.1) |  |
| Mucinous carcinoma | 2 (3.9) | 2 (4.4) | 0 |  |
| Neuroendocrine carcinoma | 1 (1.5) | 1 (2.2) | 0 |  |
| Radiotherapy | | | | |
| Whole pelvis (Gy) | | 54 | 54 | 1.00 |
| Brachytherapy (Gy) | | 28 | 28 |  |
| Chemotherapy | | | | |
| Weekly cisplatin | 41 (60.3) | 28 (60.9) | 13 (59.1) | 0.83 |
| Paclitaxel-carboplatin | 19 (27.9) | 12 (26.1) | 7 (31.8) |  |
| Cisplatin-5-fluorouracil | 8 (11.8) | 6 (13.0) | 2 (9.1) |  |
| Recurrence | 22 (32.3) | 0 | 22 (100.0) |  |
| Death | 5 (7.4) | 0 | 5 (22.7) |  |

**Fig. 1** Representative cases of cervical cancer. a F-18 FDG PET/CT images of a 47-year-old woman with stage IIB cervical squamous cell carcinoma. Trans-axial PET/CT and PET images show a mass lesion (red arrow) with high metabolic value (SUVmax, 13.7; TLG, 321.1), but low heterogeneity value (shape descriptor compacity, 1.85; GLNU from GLRLM, 27.6). The patient had no recurrence for 3 years. b F-18 FDG PET/CT images of a 42-year-old woman with stage IIB cervical squamous cell carcinoma. Trans-axial PET/CT and PET imaging revealed a mass lesion (red arrow) with relatively similar metabolic value (SUVmax, 8.4; TLG, 329.7), but relatively higher heterogeneity value (shape descriptor compacity, 2.33; GLNU from GLRLM, 94.4). The patient had disease recurrence 7 months after CCRT and subsequently died.
FDG PET/CT images of LACC patients with relatively low SUVmax and relatively high textural values. Although the stages were the same, the prognosis differed according to the ITH of the primary mass lesion.

**Prognostic value of conventional metabolic parameters, shape descriptors, and textural features for PFS and OS**

The patients included in this study were classified into two groups based on median value of PET/CT parameters such as SUVmax, MTV, TLG, shape descriptors, and textural indices. Dividing two groups based on median value of PET/CT parameter was chosen to balance the flexibility gained by adding more groups with the need to keep group sizes sufficiently large for subgroup analyses.

As summarized in Table 2, Cox regression analysis indicated that the high group of GLNU derived from GLRLM is only independent prognostic factor for PFS (HR 7.142; 95% CI 1.656–30.802; \( p = 0.008 \)) and OS (HR 9.780; 95% CI 1.222–78.286; \( p = 0.031 \)) significantly. The median PFS of patients with high and low GLNU derived from GLRLM was 8.6 and 57.7 months, respectively (\( p < 0.001 \)) (Fig. 2).

**Predictive ability of different clinical factors, metabolic parameters, shape descriptors, and textural indices for local failures and distant metastasis**

The area under the ROC curve was reported for clinical prognostic factor (stage, lymph node metastasis, tumor size), metabolic PET/CT(MTV, TLG) and GLNU derived from GLRLM as textural parameter extracted from PET/CT images (Fig. 3). Among the six parameters, GLNU derived from GLRLM (AUC 0.846, 95% CI 0.738–0.923) was the best predictor for recurrence.

| Variables | Univariate analysis | Multivariate analysis |
|-----------|---------------------|----------------------|
|           | HR  | 95% CI     | \( p \) value | HR  | 95% CI     | \( p \) value |
| **PFS**   |      |            |             |      |            |             |
| Stage (III–IVA) | 4.457 | 1.311–15.150 | 0.046 | 2.542 | 0.610–10.593 | 0.200 |
| MTV       | 4.310 | 1.586–11.713 | 0.023 | 0.630 | 0.145–2.743 | 0.539 |
| GLCM_correlation | 4.017 | 1.479–10.906 | 0.024 | 2.767 | 0.906–8.454 | 0.074 |
| GLRLM_GLNU | 8.769 | 2.579–29.822 | 0.006 | 7.142 | 1.656–30.802 | 0.008 |
| **OS**    |      |            |             |      |            |             |
| GLRLM_GLNU | 9.780 | 1.222–78.286 | 0.031 | 9.780 | 1.222–78.286 | 0.031 |

*False discovery rate (FDR)-adjusted \( p \) value after feature selection by Pearson correlation and univariate Cox analysis
Discussion

The present study demonstrated that high GLNU derived from GLRLM which is a textural parameter extracted from PET/CT images is the most prognostic factor for recurrence and OS in LACC patients receiving CCRT. Our finding that GLNU derived from GLRLM has predictive value for prognosis in LACC patients suggests that ITH may be as crucial as, or perhaps even more crucial than metabolic parameters in responses to cancer treatment. Based on such results, there might be a need for a validated prediction model incorporating textural features from PET/CT images.

In this study, we performed comprehensive analysis involving 40 features, including textural indices extracted from pretreatment PET/CT images, to identify independent prognostic markers in patients with LACC. Recently, few previous studies conducted comprehensive analysis incorporating textural features from PET/CT images related to prognosis in LACC patients who received CCRT [2, 10, 37, 38]. Lucia et al. demonstrated that GLNU from GLRLM in PET/CT and entropy from GLCM in MRI were identified as independent prognostic factors [2]. Subsequently, the authors developed a PET/MRI predictive model with textural features and validated it successfully in independent external cohorts [10]. Recently, Mu et al. showed the radiomics nomograms constructed with T stage, lymph node status, and radiomics signatures that can predict OS and PFS better than FIGO stage [37]. Esfahani et al. demonstrated that significant difference was seen between eight features in local and metastatic tumors including MTV, TLG, and entropy on PET from PET/CT [38]. All previous studies, including this, were small, and textural analysis with PET/CT can be influenced by factors that require inter-institutional standardization, such as image acquisition, reconstruction, preprocessing, segmentation, and mathematical methods [39]. Therefore, further studies are necessary.

Our findings suggest that high GLNU derived from GLRLM is only strong risk factor for recurrence and may predict recurrence of LACC better than clinical factors such as stage or conventional SUV parameters. These results are in accord with those of other studies surrounding cervical cancer and relying on PET/CT. In a retrospective cohort study of 142 patients with LACC, high gray-level run emphasis (HGRE) derived from GLRLM could predict the presence of pelvic residual or recurrent tumors most accurately, and a low HGRE (HR 4.34; p < 0.0001) were the only prognostic factors among PET/CT parameters for low OS [31]. In another cohort study, only GLNU from GLRLM was an independent predictor of recurrence and loco-regional control with significantly higher prognostic power than conventional metabolic parameters such as SUVmax and clinical factors [2]. The results of this study have clinical implications for personalized treatment in patients who may not respond well to CCRT during the course of early conventional treatment.

This study demonstrated comprehensive textural analysis with four groups of textural indices extracted from PET/CT images that had strong predictive values for recurrence, even after controlling for clinical factors such as tumor stage and size. Nevertheless, our study had certain limitations. The findings of the present study should be interpreted cautiously because they represent a retrospective study design. This study involved a relatively small cohort size and a limited number of recurrences or deaths. In addition, validation was not performed in this study. Thus, external validation with a larger independent cohort will be necessary. Finally, because textural indices from PET/CT imaging are dependent on various factors such as image acquisition, reconstruction, preprocessing, segmentation, and mathematical methods, standardization of textural analysis will be necessary in the future [39].

In conclusion, our results demonstrated that high GLNU from GLRLM on pretreatment F-18 FDG PET/CT images, were significant prognostic factors for recurrence and death in patients with LACC receiving CCRT. Based on our preliminary results, further independent validation studies should be conducted to identify high-risk patients at diagnosis using F-18 FDG PET/CT.

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Declarations

Conflict of interest No potential conflicts of interest were disclosed.

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