Research article

Value of [18F]FDG PET radiomic features and VEGF expression in predicting pelvic lymphatic metastasis and their potential relationship in early-stage cervical squamous cell carcinoma

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ABSTRACT

Purpose: The purpose of this study was to explore the value of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography ([18F]FDG PET/CT) radiomic features combined with vascular endothelial growth factor (VEGF) expression in predicting pelvic lymphatic metastasis in patients with early-stage cervical squamous cell carcinoma and the added value of radiomic features in predicting VEGF expression.

Materials and methods: Ninety-four newly diagnosed cervical squamous cell carcinoma patients (training dataset: n = 64, validation cohort: n = 30) in stage Ia to IIa, according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, who underwent [18F]FDG PET/CT were retrospectively analyzed. Radiomic features of the [18F]FDG PET scans were extracted, and the value of the lymph node sizes, metabolic parameters (both tumor and lymph nodes), radiomic features and VEGF expression level in predicting lymphatic metastasis were evaluated by receiver operating characteristics curves (ROC) and were compared using DeLong test. Moreover, we studied the associations between the [18F]FDG PET radiomic features and VEGF expression.

Results: Total lesion glycolysis (TLG) and the expression of VEGF were significantly higher in subjects with lymphatic metastasis than in those without. The homogeneity feature derived from the histogram, the skewness, had a certain value in predicting lymphatic metastasis (AUC = 0.803 in training dataset, P < 0.05, 95% CI 0.684, 0.892; AUC = 0.757 in validation dataset, P < 0.05, 95% CI 0.545, 0.904). Additionally, the combination of this radiomic feature and VEGF expression had a significantly superior predictive value (AUC = 0.878, P < 0.05, 95% CI 0.772– 0.947), compared to that of the conventional parameters. Moreover, 26 radiomic features derived from the histogram and GLCM features correlated with VEGF expression.

Conclusions: In patients with early-stage cervical squamous cell carcinoma, PLN metastasis can be predicted by TLG and the textural feature of homogeneity. Radiomic features in combination with the VEGF expression level improved the prediction accuracy. In addition, some features derived from the histogram and gray-level co-occurrence matrices (GLCM) may have a certain value in predicting the VEGF expression level.

1. Introduction

As a high-incidence malignant tumor in women, cervical cancer is a serious threat to the life and health of women. Deaths from cervical cancer account for approximately 8% of all deaths from malignant tumors in women, while more than 85% of deaths from cervical squamous cell carcinoma occur in developing countries [1].

The early clinical symptoms of cervical cancer are often not obvious. With the development of imaging technology, various imaging methods, including 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography ([18F]FDG PET/CT) in particular, have played an increasingly important role in early diagnosis, the formulation of a treatment plan and the evaluation of prognosis [2,3]. As a dual-modal imaging technique, [18F]FDG PET/CT is widely used in the diagnosis of malignant tumors. [18F]FDG-PET detects malignancies by detecting the uptake of 18F-labeled deoxyglucose into tissues [4]. Recently, a pilot study for cervical cancer showed a direct association between the metabolic parameters on [18F]FDG PET and several clinicopathological characteristics [5–8]. However, the accuracy of the diagnosis was slightly different for each study [9]. Vascular endothelial

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growth factor (VEGF) plays an important role in the occurrence and development of various malignant tumors, including cervical cancer [10,11]. Recently, metabolic parameters have been found to exhibit a certain relationship to VEGF expression, which can be used to predict prognosis [12].

With the development of radiomics, several studies have identified a relationship between the texture in CT, magnetic resonance imaging (MRI), and PET scans and clinicopathological characteristics, including the diagnosis, staging and prognosis [13–17], suggesting a potential role for [18F]FDG PET in characterizing the tumor microenvironment. However, similar research in cervical squamous cell carcinoma is rare. To our knowledge, no studies have reported a correlation between the [18F]FDG PET texture and the tissue expression of VEGF. Our aim was to explore the value of the [18F]FDG PET texture combined with VEGF expression in predicting pelvic lymphatic metastasis in patients with early-stage cervical squamous cell carcinoma and the added value of texture in predicting VEGF expression.

2. Materials and methods

2.1. Patients

Ninety-four newly diagnosed cervical squamous cell carcinoma patients who had undergone a radical hysterectomy in our hospital and had received pretreatment [18F]FDG PET/CT or staging were retrospectively analyzed between January 2014 and September 2015. The inclusion criteria were as follows: pathologically proven cervical squamous cell carcinoma; the absence of distant metastasis or other malignant tumors; no treatments prior to surgery; and normal serum glucose levels before undergoing PET/CT. The final study of 94 patients divided into two groups including training dataset and the validation dataset.

2.2. Immunohistochemistry

All the cervical squamous cell carcinoma tissue sections were prepared by the department of pathology in our hospital. A Leica BOND-MAX™ automatic staining machine (Leica Company, Germany) was used for the immunohistochemical staining. A polyclonal antibody directed against VEGF (Abcam, Shanghai) was diluted to a 1:50 working solution. A 20-min incubation in ER1 liquid was used for antigen recovery. The dewaxing, antigen epitope exposure, and blocking procedures, the incubation with the primary antibody, the development of the DAB oxidation color, hematoxylin staining and dehydration were automatically completed by the computer. Next, 3 high-magnification (400×) fields were randomly manually selected from each section using the NIS-Elements F 3.2 image acquisition software. Using the Image-Pro Plus 6 software, each image was analyzed, and the integrated optical density accumulative value (IOD sum) was measured. The average IOD sum value of three visual fields was used to represent the staining intensity of the section.

2.3. [18F]FDG PET/CT acquisition and texture extraction

All the patients fasted for more than 6 h before the [18F]FDG PET/CT scans were performed. Their serum glucose level was controlled to less than 7 mmol/l. [18F]FDG (produced by MiniTrace II and TracerLab FX-FDG, purity > 99%; GE Healthcare, Waukesha, Wisconsin, USA) was injected at a dose of 3.7 MBq/kg. The patients rested quietly for 60 min before the PET/CT (Discovery PET/CT 690; GE Healthcare, USA) scanning. All the whole-body CT and PET scans were acquired with free breathing for attenuation correction and image fusion. First, low-dose non-enhanced CT images were acquired from the top of the skull to the mid-thigh, with a bulb voltage of 120 kV, auto mA (30–210 mA; noise index 25), and a slice thickness of 3.27 mm, for the attenuation correction of the PET images. Then, the PET data were

acquired immediately after the CT scan using a three-dimensional acquisition mode at a speed of 1.5 min/bed (7–8 beds in total) and a matrix size of 192 × 192. The attenuation-corrected PET images were reconstructed using an ordered-subsets expectation maximization iterative reconstruction algorithm, with 24 subsets and two iterations. The time-of-flight and point-spread function techniques were also used in the reconstruction.

A volume of interest (VOI) was automatically obtained on an AW4.5 workstation (GE Healthcare, USA). The maximum of the standard uptake value (SUVmax), SUVmean, metabolic tumor volume (MTV), the total lesion glycolysis (TLG) were measured automatically inside the segmented VOI. A short-axis diameter ≥ 10 mm with positive FDG uptake (SUVmax ≥ 3.5) was considered to be a metastatic lymph node in PET/CT [18] and short-axis diameter and SUVmax of these lymph nodes were also measured.

Using the "halo method," a region of interest (ROI) based on the PET images was manually drawn around the cervical squamous cell carcinomas by two nuclear medicine physicians, independently, who had more than 5 years of experience and were blinded to the patients' clinical data [19]. When the two physicians disagreed, they reached an agreement through negotiation. The texture parameters were extracted from the [18F]FDG PET images using A.K. (Artificial Intelligent Kit, GE Healthcare, China) software. The first-order features based on the histogram analysis were measured by identifying the intensity distribution on the original image, including the mean, uniformity, variation, skewness, kurtosis and so on. The high-order textural features were measured using the gray-level co-occurrence matrices (GLCM), the gray-level run-length matrix (GLRLM), the gray-level size zone matrix (GLSZM) and the form factor parameters.

2.4. Statistical analysis

The results are expressed as averages and ranges for quantitative variables, while numbers and percentages are used for categorical findings. If the quantitative data satisfied a normal distribution, a t-test was used to compare differences between the subgroups, otherwise a *Mann-Whitney U* test was used.

The relationship between VEGF expression, metabolic parameters and the lymphatic metastasis of early-stage cervical squamous cell carcinomas was analyzed using a receiver operating characteristic (ROC) curve. The optimal cutoff threshold values were automatically determined at the point on the ROC curve at which sensitivity added specificity was maximal.

Combination prediction was constructed using multivariate logistic regression. The value of the lymph node sizes, metabolic parameters (both tumor and lymph nodes), radiomic features and VEGF expression level in predicting lymphatic metastasis were evaluated by ROC curves and were compared using DeLong test. The correlations between VEGF expression and the textural features were examined using Spearman's correlation coefficient, with the alpha level set at 0.05.

The results were considered statistically significant at the 5% critical level (P < 0.05). All the statistical analyses were performed using SPSS (version 22.0, IBM, Armonk, NY) and MedCalc (version 15.2.2, MedCalc Software bvba, Ostend, Belgium).

3. Results

The clinicopathological characteristics are summarized in Table 1. A total of 94 patients divided into two groups including training dataset with 64 patients with a median age of 48.41 years (range 28–70 years) and the validation dataset with 30 patient with a median age of 47.4 years (range 31–62 years). The FIGO staging all ranged from Ia to IIa. 23 patients had lymphatic metastasis in training dataset that was pathologically proven (23/64) and 10 patients (10/30) in validation dataset.