Relationship of ^{18}F-FDG PET/CT metabolic, clinical and pathological characteristics of primary squamous cell carcinoma of the cervix

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ABSTRACT

The objectives of this retrospective study were to use preoperative ^{18}fluoro-D-glucose (^{18}FDG) PET/CT in patients with primary cervical squamous cell carcinoma to explore the relationship between clinical, pathological and metabolic characteristics. Eighty consecutive patients with squamous cell carcinoma of cervix received ^{18}FDG PET/CT scan before treatment. Metabolic tumor volume (MTV), total lesion glycolysis (TLG) and the peak standardized uptake value (SUVpeak) of the cervical tumors were calculated by an iterative adaptive algorithm. The association of these metabolic markers with serum squamous cell carcinoma antigen (SCC-ag), International Federation of Gynecology and Obstetrics (FIGO) stage, maximum tumor size and depth of cervical stromal invasion of the tumor was determined by the multivariate analysis. MTV and TLG were significantly higher in subjects with serum SCC-ag levels ≥3.95, with FIGO stage 1b2 and with a maximum tumor size of ≥4 cm ($p \leq 0.009$). Higher SUVpeak levels were associated with a maximum tumor size of ≥4 cm and with a cervical stromal invasion depth of ≥1/2 ($p \leq 0.003$). Multivariate analysis indicated that MTV was independently associated with FIGO stage Ib2 ($p=0.041$) and depth of cervical stromal invasion ($p=0.020$). TLG and SUVpeak were independently associated with maximum tumor size ($p \leq 0.004$) and depth of cervical stromal invasion ($p \leq 0.013$). Significant linear correlation was found between SUVpeak and tumor size; the Pearson correlation coefficient was 0.34 ($p=0.002$). Metabolic parameters such as MTV, TLG and SUVpeak are able to predict clinical and pathological status in preoperative cervical cancer.

Significance of this study

What is already known about this subject?

- Fluoro-D-glucose (FDG) PET/CT facilitates decision-making and radiation treatment planning and provides important information about treatment response.
- FDG PET/CT imaging with novel radiopharmaceutical could further affect cervical cancer treatment as surrogate markers of drug activity.
- PET/CT was more efficient in detecting recurrence and finding more lesions.

What are the new findings?

- MTV and TLG were significantly higher in subjects with serum SCC-antigen levels.
- Higher peak standardized uptake value (SUVpeak) levels were associated with a maximum tumor size of >4 cm and with a cervical stromal invasion depth.
- Significant linear correlation was found between SUVpeak and tumor size.

How might these results change the focus of research or clinical practice?

- MTV, TLG and SUVpeak are able to predict clinical and pathological status in preoperative cervical cancer.

INTRODUCTION

Cervical cancer is the second most common malignancy in women worldwide.[1] In China, cervical cancer is the leading gynecological cancer in women with an estimated 131 500 new cases in 2010.[1] 18Fluoro-D-glucose (^{18}FDG) PET/CT is used to quantitatively evaluate the clinical and prognostic status of cervical cancer on the basis of ^{18}F-FDG uptake, and plays an important role in the differential diagnosis, staging and decision-making of clinical therapy of cervical cancer.[2] The standardized uptake value (SUV) of ^{18}FDG is the most common, convenient and semiquantitative parameter used to quantify malignancies.[2] Studies have confirmed that the higher the maximum SUV (SUVmax), the poorer the clinical manifestations, prognosis and response to therapy.[3–7] 18FDG PET/CT can be used to determine metabolic tumor volume (MTV) and total lesion glycolysis (TLG); MTV refers to the increase in ^{18}F-FDG uptake which reflects glucose metabolism[2] and TLG represents the metabolic load of malignant tumors which is dependent on the volume and glucose use of a tumor.[2]

Squamous cell carcinoma antigen (SCC-ag) is a serological tumor marker for women with squamous cell carcinoma of the cervix.[8–10] The level of SCC-ag is elevated in 28–86% of patients with squamous cell carcinoma.[3] SCC-ag levels prior to treatment can predict lymph node involvement, response to therapy and after therapy can predict survival outcomes

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and risk of recurrence.[11–16] Serum SCC-ag level is closely related to the size, stage, degree of invasion and lymph node metastasis of cancers.[6]

Optimal management of cervical cancer requires clinical staging, appropriate treatment and effective post-therapy surveillance.[17] The use of ^{18}FDG PET/CT to determine the disease state and prognosis is dependent on the accuracy of the quantification of the metabolic parameters. In this study, we used the PET Volume Computerized Assisted Reporting (PET VCAR2; GE Healthcare AW Station, General Electric, Milwaukee, Wisconsin, USA) software that uses an iterative adaptive algorithm to better quantify the volume-based quantitative metabolic parameters MTV, TLG and SUVpeak of ^{18}FDG PET/CT before surgery. We also investigated the association of these metabolic parameters with a number of clinical and pathological outcomes in patients with primary cervical squamous cell carcinoma using multivariate analysis.

MATERIALS AND METHODS

Patients and study design

This was a retrospective medical record review of consecutive patients with squamous cell carcinoma of the cervix being treated at Shengjing Hospital of China Medical University (Shenyang, China) from January 2011 to January 2013. There was a 6-month follow-up period. The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Shengjing Hospital.

Patients included in the study had Ib-IIa cervical cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The stage of cancer was confirmed by gynecologic examination for each patient. None of the patients received antitumor therapies, chemotherapy or radiotherapy before surgery.

At 1 week before surgery (mean±SD 6.5±1.32 days), patients underwent ^{18}FDG PET/CT and were evaluated for the presence of serum SCC-ag. For the detection of SCC-ag, venous blood (3 mL) was collected and serum was separated and detected with an automated fluorescence detector. Microparticle enzyme immunoassay was performed to detect the titer of SCC-ag, with ≤1.0 ng/mL being used as the reference for normal SCC-ag levels. Pathological examination was performed after surgery, and the following information was recorded: pathological type, pathological grade, cancer size and depth of invasion. Tumor size was determined by the maximum length of diameter of measured tumor.

PET/CT and image analysis

All patients in this study received an ^{18}F-FDG PET/CT scan. Prior to ^{18}F-FDG PET/CT, patients fasted for >6 hours and water intake was encouraged. Fasting helped to homogenize the insulin state of a person. Patients voided their bladder prior to imaging, and the pelvis was imaged first. A blood glucose level determined to be <7 mmol/L. ^{18}FDG (MiniTrace II and TraceLab FXFDG; GE, USA; purity>99%) (3.7–5.55 MBq/kg (0.1–0.1 5mCi/kg)) was injected intravenously, followed by a 60 min uptake period. Low-dose CT (120–140 kV, 80 mA) and PET (for CT/PET scan, Discovery Elite; GE, USA) scans were then obtained from the top skull to midthigh (2 min/bed position) with the arms up, followed by dedicated images of the head and neck (5 min/bed position) with the arms down. All images were reviewed on an AW4.6 workstation (GE Healthcare) that allowed multiplanar reformatting of images. Images were processed using the PET VCAR software (PET Volume Computerized Assisted Reporting) on an Advantage Workstation (GE Healthcare) to automatically detect the metabolic parameters of the cancer (SUVpeak, MTV and TLG).

Statistical analysis

Continuous variables were presented as means and SDs. Categorical variables were presented as counts and percentages. Independent t-tests were performed for the comparisons between two groups. One-way analysis of variance with Bonferroni post hoc tests were used for comparisons among three or more groups. Univariate linear regression and multivariate linear regression were performed to detect the factors that influenced MTV, TLG and SUVpeak. Factors that showed statistically significant differences in univariate analysis were included in multivariate analysis with stepwise model selection to further detect the influencing factors. MTV, TLG and SUVpeak were separately used as the dependent variable in each model. Since four factors were set as the predictors (see below) and the R^2 (0.199–0.246) was in the multivariable linear regression models, the sample size ranged from 42 to 54. The sample size in this study was 80; hence, the size of the study sample was sufficient for this method. Statistical analysis was considered significant as the two-sided p value of <0.05. Statistical analyses were performed by the SPSS software V.17 (SPSS, Chicago, Illinois, USA).

RESULTS

Demographic distribution of subjects

A total of 80 subjects with a mean age of 48.3 years were included in this study. The mean MTV, TLG and SUVpeak were 10.85 cm^3, 97.31 g/mL cm^3 and 11.11 g/mL, respectively. The mean serum SCC-ag value was 3.94, and the mean maximum tumor size was 3 cm. Thirty-eight subjects had FIGO stage Ib1 tumors, and the majority (56 subjects) had a depth of cervical stromal tumor invasion ≥1/2 (table 1).

MTV analysis

The mean MTV was significantly higher in subjects with serum SCC-ag levels ≥3.95 compared with those with serum SCC-ag levels <3.95 (p=0.008) (table 1). MTV was also higher in subjects with FIGO stage at Ib2 compared with those at Ib1 and IIa cancer (p≤0.023) and in subjects with maximum tumor size ≥4 cm compared with those with <4 cm (p=0.012). MTV was significantly higher in subjects with a cervical stromal invasion depth of ≥1/2 compared with those with a cervical invasion depth of <1/2 (p=0.001) (table 1).

Univariate analysis indicated that serum SCC-ag level, FIGO stage Ib2, maximum tumor size and depth of cervical stromal invasion significantly affected MTV (p≤0.008) (table 2). Consequently, these four variables were included in the multivariate model. After the stepwise model selection, FIGO stage and cervical stromal invasion depth were found significantly associated with MTV; the

Table 1 Distribution of the MTV, TLC and SUV peaks

		MTV		TLG		SUVpeak	
	N	Mean±SD	p Value	Mean±SD	p Value	Mean±SD	p Value
Serum SCC-ag							
<3.95	60	9.22±8.38	0.008	80.22±91.11	0.009	10.77±6.85	0.400
≥3.95	20	15.73±11.44		148.59±117.5		12.13±3.61	
FIGO stage							
Ib1	38	7.62±5.36	<0.001	61.88±62.3	0.001	9.41±5.36	0.062
Ib2	14	19.01±15.82*		172.06±156.34*		13.07±6.74	
IIa	28	11.14±7.73†		108.02±92.65		12.43±6.6	
Tumor maximum size (cm)							
<4	59	8.88±7.88	0.012	72.77±78.95	0.004	9.77±5.13	0.001
≥4	21	16.38±11.82		166.26±127.55		14.86±7.48	
Cervical stromal invasion depth							
<1/2	24	5.67±4.6	0.001	41.11±56.09	<0.001	8.01±6.22	0.003
≥1/2	56	13.07±10.32		121.39±108.01		12.44±5.76	

*p<0.05, significantly different compared with Ib1.
†p<0.05, significantly different compared with Ib2.
FIGO, International Federation of Gynecology and Obstetrics; MTV, metabolic tumor volume; SCC-ag, squamous cell carcinoma antigen; SUV, standard uptake volume; TLG, total lesion glycolysis.

mean MTV increased by 7.5 cm^3 in subjects with FIGO stage at Ib2 compared with those with stage Ib1 (p=0.041) and increased 5.24 cm^3 in subjects with a cervical stromal invasion depth of ≥1/2 compared with those with stromal invasion depth of <1/2 (p=0.02; table 2).

TLG analysis

The mean TLG was significantly higher in subjects with serum SCC-ag values ≥3.95 compared with those with serum SCC-ag values <3.95 (p=0.009) and in subjects with FIGO stage Ib2 compared with those at Ib1 cancer (p=0.001). TLG was also higher in subjects with a maximum tumor size of ≥4 cm compared with those with a tumor size of <4 cm (p=0.004) and in subjects with a cervical stromal invasion depth of ≥1/2 compared with those with an invasion depth of <1/2 (p<0.001; table 1).

Univariate analysis found that serum SCC-ag level, FIGO stage, tumor maximum size and cervical stromal invasion depth were all significantly affected TLG and subsequently all four were included in the multivariate model. After the stepwise model selection, tumor maximum size and cervical stromal invasion depth were found to be significantly associated with TLG; the mean TLG increased by 79.73 g/mL cm^3 in subjects with a maximum tumor size of ≥4 cm compared with those with a maximum tumor size of <4 cm (p=0.001), and increased by 64.62 g/ml cm^3 in subjects with a cervical stromal invasion depth of ≥1/2 compared with subjects with a stromal invasion depth of <1/2 (p=0.005; table 3).

Table 2 Results of univariate and multivariate linear regression in MTV*

	Univariate regression		Multivariate regression	
	β±SE	p Value	β±SE	p Value
Serum SCC-ag				
<3.95	Reference			
≥3.95	6.5±2.38	0.008		
FIGO stage				
Ib1	Reference		Reference	
Ib2	11.39±2.74	<0.001	7.5±3.61	0.041
IIa	3.52±2.19	0.111	1.83±2.26	0.420
Tumor maximum size (cm)				
<4	Reference			
≥4	7.5±2.3	0.002		
Cervical stromal invasion depth				
<1/2	Reference		Reference	
≥1/2	7.4±2.2	0.001	5.24±2.2	0.02

*Factors that showed statistically significant differences in univariate analysis were included in multivariate model with stepwise model selection to further detect the influence factors. The results of stepwise model selection were presented in multivariate analysis.
FIGO, International Federation of Gynecology and Obstetrics; MTV, metabolic tumor volume; SCC-ag, squamous cell carcinoma antigen.

Results of SUVpeak

The mean SUVpeak was significantly higher in subjects with a maximum tumor size of ≥4 cm compared with those with a tumor size of <4 cm (p=0.001) and in subjects with a cervical stromal invasion depth of ≥1/2 compared with those with a tumor invasion depth of <1/2 (p=0.003). There were no significant differences in SUVpeak in serum SCC-ag level and FIGO stage groups (p>0.05; table 1).

Univariate analysis showed that maximal tumor size and cervical stromal invasion depths significantly affected SUVpeak and were included in the multivariate model. After the stepwise model selection, both parameters were found to be significantly associated with SUVpeak (table 4). The mean SUVpeak increased by 4.32 g/mL in subjects with a maximum tumor size of ≥4 cm compared with patients with a maximum tumor size of <4 cm (p=0.004). SUVpeak also increased by 3.57 g/mL in subjects whose cancer had a cervical stromal invasion depth of ≥1/2 compared with subjects with a stromal invasion depth of <1/2

Table 3 Results of univariate and multivariate linear regression in TLG*

	Univariate regression		Multivariate regression	
	β±SE	p Value	β±SE	p Value
Serum SCC-ag				
<3.95	Reference			
≥3.95	68.38±25.35	0.009		
FIGO stage				
Ib1	Reference			
Ib2	110.18±29.66	<0.001		
IIa	46.14±23.63	0.054		
Tumor maximum size (cm)				
<4	Reference		Reference	
≥4	93.5±23.85	<0.001	79.73±23.29	0.001
Cervical stromal invasion depth				
<1/2	Reference		Reference	
≥1/2	80.28±23.34	0.001	64.62±22.36	0.005

*Factors that showed statistically significant differences in univariate analysis were included in multivariate model with stepwise model selection to further detect the influence factors. The results of stepwise model selection were presented in multivariate analysis.
FIGO, International Federation of Gynecology and Obstetrics; SCC-ag, squamous cell carcinoma antigen; TLG, total lesion glycolysis.

Table 4 Results of univariate and multivariate linear regression in SUV peak*

	Univariate regression		Multivariate regression	
	β±SE	p Value	β±SE	p Value
Serum SCC-ag				
<3.95	Reference			
≥3.95	1.36±1.61	0.4		
FIGO stage				
Ib1	Reference			
Ib2	3.66±1.9	0.058		
IIa	3.02±1.51	0.049		
Tumor maximum size (cm)				
<4	Reference		Reference	
≥4	5.09±1.48	0.001	4.32±1.46	0.004
Cervical stromal invasion depth				
<1/2	Reference		Reference	
≥1/2	4.42±1.44	0.003	3.57±1.4	0.013

*Factors that showed statistically significant differences in univariate analysis were included in multivariate model with stepwise model selection to further detect the influence factors. The results of stepwise model selection were presented in multivariate analysis.
FIGO, International Federation of Gynecology and Obstetrics; SCC-ag, squamous cell carcinoma antigen; SUV, standard uptake volume.

(p=0.013). Significant linear correlation was found between SUVpeak and tumor size; the Pearson correlation coefficient was 0.34 (p=0.002).

DISCUSSION

^{18}FDG PET/CT is a non-invasive imaging technique that is widely used in the diagnosis and monitoring of cancers such as cervical cancer. In this retrospective study, ^{18}FDG PET/CT was used preoperatively in patients with primary cervical squamous cell carcinoma, and the association of MTV, TLG and SUVpeak with FIGO stage, SCC-ag value, postoperative cancer size and invasion depth was evaluated. Multivariate analysis indicated that FIGO stage and stromal invasion depth of the cervical cancer were associated with MTV. Multivariate analysis showed that TLG and SUVpeak were associated with maximum tumor size and stromal invasion depth. We found no relationship of SUVpeak with SCC-ag levels. These findings suggest that the MTV, TLG and SUVpeak values before surgery may reflect the cancer load and invasiveness of cervical squamous cell carcinoma and may help to predict the clinical pathology and treatment response of cervical cancer.

An important part of this study was the use of the iterative adaptive algorithm and the PET VCAR software[18] to automatically quantify MTV and SUVpeak. PET VCAR is an automated segmentation software system that uses an iterative adaptive algorithm to detect the threshold level that separated the target volume from the background tissue by weighting the SUVmax and the SUVmean within the target volume with a weighting factor set at 0.5. SUVmax was defined as the maximum SUV within the target volume, and SUVmean was the sum of SUV in each voxel in the target volume divided by the number of voxels within the target volume. SUVpeak represents the mean maximal value of SUV within 1 cm^3. MTV was specified as the contoured tumor tissue showing active FDG uptake, and TLG was defined as the product of SUVmean and MTV. Our study demonstrates that this approach can accurately give tumor metabolic information which can help to predict patient's clinicopathological features and treatment response.

Other studies have also found an association of MTV, TLG and SUVmax with clinical and pathological features of cervical cancer. In a retrospective analysis of 287 patients with primary cervical cancer (FIGO stages IA2–1VB) who received preoperative ^{18}FDG PET/CT, SUVmax was markedly related to an increased risk of lymph node metastasis (p=0.0009).[4] The study found no association of SUVmax with tumor volume but did find that SUVmax was an independent risk factor for death. Another study showed that SUV of pelvic lymph nodes was significantly related to the risk for pelvic recurrence of cervical cancer.[19] Similar to our study, one study found that preoperative SUVmax of primary cervical cancer was closely related to FIGO stage and extent of invasion.[20] They also found that SUVmax was associated with lymph node metastasis and tumor size. In addition, a study conducted by Crivellaro *et al*[18] on 89 patients with early cervical cancer revealed that the MTV and TLG were significantly higher in pN1 cancer than in pN0 stage cancer (p=0.0006 and p=0.03, respectively).

Similar to our study, Pan *et al*[5] found that SUVmax of primary cervical cancer was not associated with preoperative SCC-ag levels. Pan *et al* did find that the higher the SUVmax of primary cancer, the poorer the prognosis. They also found that higher SCC-ag values not only suggested a poor prognosis but also indicated a high risk for recurrence following therapy.

SUVmax is a common metabolic parameter used to evaluate the clinical and pathological features of primary cervical cancer before surgery. However, SUVmax is

calculated according to pixel intensity; a single pixel region of interest (ROI) approximately equals to 10.43 mm^2 or 34.2 mm^3. SUVpeak refers to the mean maximal SUV within 1 cm^3 and 1.5 cm ROI. SUVpeak is more stable than SUVmax and less influenced by pixel intensity.[21] Our results showed that SUVpeak was positively related to FIGO stage and invasion depth, suggesting that SUVpeak may also serve as a reliable metabolic parameter reflecting the clinicopathological features of primary cervical cancer. In addition, our findings indicate that SUVpeak had no relationship with SCC-ag levels, which is consistent with what was reported by Nakamura *et al*[3] for SUVmax.

MTV and TLG reflect the degree of glucose metabolism of tissues, including cancer, and may avoid some of the limitations of SUV, which is based on one of the clinical cancer size in images. However, active glucose metabolism can be misleading as some normal tissues may show high ^{18}FDG uptake.[2 6]

FDG PET/CT has been found useful in the detection of locoregional and distant nodal metastases, as well as in the characterization of tumor metabolism and invasion depth in cervical cancer.[22] It has played a role in changing disease management, such as facilitating radiation planning.[22] SUVmax, MTV and TLG are emerging as predictive markers and possible stratification tools for treating cervical cancer. For patients with early cervical cancer (small cancer, an invasion depth of <1/2 and no lymph node metastasis), whether fertility-conserving surgery is conducted requires further investigation and clinical follow-up. FDG PET/CT provides important information about treatment response, disease recurrence and long-term survival.[22]

This study had several limitations. This was a retrospective chart review with a small sample size. Larger prospectively defined randomized studies are needed to further characterize the correlation of MTV, TLG and SUVpeak with clinicopathological features and disease characteristics of cervical cancer. Longer studies looking at long-term survival and disease recurrence would also be of interest to further characterize the use of ^{18}F-FDG PET/CT in monitoring disease and treatment outcomes. Also we did not evaluate the association of MTV, TLG and SUVpeak values with lymphovascular and lymph node metastasis which may have given further insight into how MTV, TLG and SUVpeak values reflect cancer load and invasiveness. The observation that SUVpeak showed low association with SSC-Ag may be due to poor reducibility of the method and not lack of a true relationship. The coefficient of variation in SUV peak of serum SCC-ag <3.95 was 63.6%, and SUV peak of serum SCC-ag ≥3.95 was 29.8%. The subjects with serum SCC-ag <3.95 had much more variability relative to the mean of SUV peak compared with those with serum SCC-ag ≥3.95. The mean MTV is 10.85 cm^3 and the partial volume effect was likely to have played a part. Prior to ^{18}F-FDG PET/CT, we requested patients to fast for >6 hours to assure that the insulin state was similar in different tissues. In this study, follow-up was only 6 months and some of the records were incomplete which may have confounded the results. Consequently, we did not present data from the follow-up period. The use of SCC-ag level to evaluate the presence of cervical cancer is not universally accepted. However, many studies have shown an association of the levels of SCC-ag with cervical cancer, but the levels do not always reflect prognosis, recurrence or response to treatment.[11–16 23–28] Further work is required to establish the use of SCC-ag levels in characterizing cervical cancer. We acquired PET/CT scans from the top of the skull to the midthigh to evaluate the presence of cancer in most of the patient's body using FDG uptake. The brain is a high glucose-using organ. To compensate for this, we shortened the time of the head scan so as to obtain informative data. This approach has been used in prior studies.[18 29 30]

In summary, our study found that MTV, TLG and SUVpeak as determined by ^{18}FDG in PET/CT correlated with several clinicopathological features of primary squamous cell cervical cancer and may give clinical insights into preoperative stage, cancer size and invasion depth.

Contributors WX undertook the statistical analysis, wrote the first draft of the manuscript. SY performed research/study. JX managed the literature searches and analyses. QG designed the study and wrote the protocol.

Competing interests None declared.

Ethics approval The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Shengjing Hospital.

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