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Tumor and metastatic lymph nodes metabolic activity on ^{18}F-FDG-PET/CT to predict progression-free survival in locally advanced cervical cancer

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Abstract

Objective The present study investigated the predictive diseases progression value of preoperative fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients with local advanced cervical cancer (LACC).

Methods In total, 267 patients [median age 58 (range: 27–85) years old] with LACC underwent ^{18}F-FDG PET/CT prior to any treatment. The maximum standardized uptake values (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary lesion and metastatic lymph nodes were measured on PET/CT and correlated with clinicopathological features and progression-free survival (PFS).

Results The median follow-up was 36.52 (range: 3.09–61.29) months. During the observation period, 80 (30.0%) patients exhibited disease progression. Univariate analysis showed that FIGO stage, concurrent chemoradiotherapy (CRT), serum level of carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC-Ag), primary tumor MTV (pMTV) and TLG (pTLG), lymph nodes SUV_{max} ($nSUV_{max}$) and TLG (nTLG), and total metabolic activity (sMTV, sTLG) were associated with PFS. $nSUV_{max} \geq 5.29$, CEA ≥ 7.11 ng/ml and deficiency of concurrent CRT were independent risk factor for PFS ($p = 0.006$, $p = 0.008$, $p = 0.014$). The 3-year PFS for patients with high $nSUV_{max}$ were 42.2% compared to 56.3% for low $nSUV_{max}$ values.

Conclusion Pretreatment cervical and lymph nodes metabolic parameters were associated with PFS in patients with LACC.

Keywords Cervical cancer · ^{18}F-FDG PET/CT · Metabolic parameters · Progression-free survival

Introduction

Cervical cancer is one of the most common malignancies and the fourth leading cause of cancer-related death in women worldwide [1, 2]. Although often curable if detected early, almost half of the patients present locally advanced cervical cancer (LACC) at the time of diagnosis. The current standard treatment modality for patients with LACC, based on International Federation of Gynecology and Obstetrics (FIGO) staging IIB–IVA, is concomitant chemoradiation therapy (CRT) using a cisplatin-based regimen with pelvic external beam radiotherapy (EBRT) and subsequent brachytherapy (BT) [3, 4]. Despite the well confirmed contribution of CRT toward improved survival outcomes with a complete clinical response achieved in 70%–90% patients [5], about one-third of patients experience disease recurrence within 2 years after therapy completion [6]. Therefore, to optimize treatment plans and improve risk-adapted treatment strategies, data regarding whether patients can achieve long-term disease-free survival through treatment are essential.

As a functional multimodality imaging system, fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has played a well-established role in the management of patients with malignant tumors, especially in clinical staging, observation of curative effect, and analysis of the prognosis for LACC based on American National Comprehensive Cancer Network guidelines [3, 7].

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Recent attention has focused on the prognostic value of metabolic parameters from pretreatment ^{18}F-FDG PET/CT in cervical cancer, including the maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Some studies reported a longer survival in patients with negative versus positive PET findings [8], and the volume-based parameters (MTV and TLG) of the primary tumor are predictors of event-free and overall survival(OS) in cervical cancer patients treated with CRT [9, 10]. Other studies revealed that lymph node metabolic activity on ^{18}F-FDG PET/CT can help clinicians more comprehensively judge prognosis [10]. The role of ^{18}F-FDG PET/CT as a prognostic biomarker for patients with LACC remains controversial [11], however, and a comprehensive analysis of the relationship between semi-quantitative metabolic parameters and inferior outcomes is needed [12].

In this context, we aimed to evaluate the prognostic value of multiple metabolic parameters from preoperative ^{18}F-FDG PET/CT in patients with LACC and to investigate the prognostic values of clinicopathologic features to stratify patients with cervical cancer and determine individualized treatment.

Materials and methods

Patients

This study was approved by an Investigational Review Board of The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), the IRB number is IRB-2022-423. The requirement to acquire informed consent was waived by the Ethics Committee of Zhejiang Cancer Hospital. Consecutive patients between June 2016 and March 2019 in Zhejiang Cancer Hospital were retrospectively selected and enrolled using the following inclusion criteria: (1) histologically proven cervical cancer based on examination of biopsy specimens and staged IIB–IVA by 2014 FIGO staging; (2) determination of CRT or radical radiotherapy as the primary treatment modality; (3) no prior treatment before ^{18}F-FDG PET/CT scan; and (4) availability of complete medical history and clinicopathological data. The exclusion criteria were as follows: (1) secondary malignant disease; (2) serious infection or inflammation(which were found out mainly based on some clinical findings, such as lab data, imaging, and their medical history.); or (3) hepatic or renal dysfunction. Data from 267 patients constituted the final clinical database. Figure 1 shows the flowchart of selection criteria.

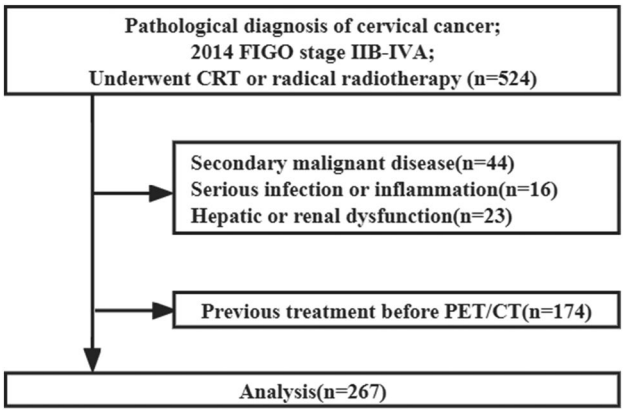

Fig. 1 Flow diagram outlining criteria used for patient inclusion and exclusion

^{18}F-FDG PET/CT acquisitions

Whole body acquisition was performed in 2–3 min/bed using a hybrid system (GE Discovery PET/CT 710, GE Healthcare, Boston, MA, USA) that covered the area from the base of the skull to the upper thigh after intravenous injection of about 3.7 MBq/kg of ^{18}F-FDG. All patients fasted for at least 6 h previously and presented with a blood glucose concentration < 10 mmol/L. The reconstruction used an attenuation-weighted ordered-subsets expectation maximization iterative algorithm with 4 iterations and 8 subsets, a Gaussian filter with 4.0-mm full width at half maximum, and scatter correction.

Imaging interpretation

Two experienced nuclear physicians interpreted the images and data for each patient using a GE EBW workstation. There was no significant difference between the two readers in metabolic indicators for primary tumor and positive lymph nodes, and intra class correlation coefficient (ICC) demonstrated well inter-observer agreement at 0.81 and 0.83. The SUV_{max}, MTV, and TLG were assessed for the primary lesion and metastatic lymph nodes, and these parameters were determined in a three-dimensional manner using the same vendor-provided software (GE). The MTV was estimated by selecting the volume of interest (VOI) on the axial image; the size of the VOI was checked on the corresponding coronal and sagittal images to ensure it included the entire active tumor in the VOI. To define the contouring margins around the target lesion, we used the percentage of SUV_{max} of 40% as a central value and a margin threshold to delineate the lesion edge [13]. The SUV_{max} was calculated with this equation:

(decay-corrected activity/tissue volume)/(injected dose/body weight). The TLG was calculated by multiplying mean standardized uptake values (SUV_{mean}) and MTV. A positive diagnostic standard for lymph node metastasis was required to meet both the lymph node short diameter > 0.5 cm and $SUV_{max} > 2.5$.

The SUV_{max}, MTV, and TLG of primary tumors were marked as pSUVmax, pMTV, and pTLG, respectively. The maximum SUVs of metastatic pelvic and para-aortic lymph nodes (PALN) were marked as $nSUV_{max}$; nMTV and nTLG were calculated for all metastatic lymph nodes. The sMTV was defined as the sum of pMTV and nMTV, and the sum of pTLG and nTLG was marked as sTLG.

Treatment and follow-up

All patients underwent pelvic ± lombo-aortic EBRT based the 2015 National Comprehensive Cancer Network guidelines. Delivery was by intensity-modulated radiation therapy, volumetric-modulated arc therapy, or helical tomotherapy administered to the whole pelvic region in 25–28 fractions of 1.8 Gray (Gy) for a total dose of 45–50.4 Gy. For patients with para-aortic nodal involvement, the superior border extended to the level of renal vessels or to the upper margin of the twelfth thoracic vertebra. In cases of significantly enlarged and undetected lymph nodes, additional radiotherapy with a highly conformal EBRT was required, with an additional 10–15 Gy. Concomitant chemotherapy with cisplatin 40 mg/m^2 was administered weekly during EBRT for 3–6 courses. The treatment was then completed with an additional pulse dose rate BT, which was delivered with an iridium-192 source, with 24–36 Gy (biologically effective dose 38.4–57.6 Gy) in 4–6 fractions to point A. For a small number of patients, radical radiotherapy alone was administered.

Follow-up was performed 1 month after radical chemoradiotherapy, every 3–6 months for 2 years, and every 6–12 months for 3–5 years after treatment. Disease progression was determined by gynecologic examination, serum tumor markers, and enhanced abdominopelvic CT with or without follow-up ^{18}F-FDG PET/CT(When abdominopelvic CT scan could not show suspicious lesion, PET/CT can be used in addition as for its advantage of whole-body scan and offering metabolic information.). For cases in which clinical assessment, serum tumor markers or imaging studies revealed any abnormality, additional diagnostic studies or pathological confirmation were performed to evaluate cancer progression. Progression-free survival (PFS) was calculated from the date of biopsy results to disease progression, relapse, mortality from any causes, or the most recent follow-up date.

Statistical analysis

Statistical analysis was performed using SPSS software (version 23, IBM, Armonk, NY, USA). Data were presented as median (range). The relationships between clinicopathological characteristics, PET/CT parameters, and cancer progression of were analyzed using the chi-square test. A maximally selected log-rank statistics approach was used to perform a cut-off point analysis. Univariate and multivariate analyses with clinicopathologic factors were performed to assess the association of PFS and metabolic ^{18}F-FDG PET/CT parameters using the Kaplan–Meier method with log-rank test and Cox proportional hazards model, respectively. Survival curves were generated using Kaplan–Meier estimates, and the significance of difference between survival curves was tested using log-rank tests. All p values were 2-sided, and a value of $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

A summary of patient characteristics is shown in Table 1. Based on inclusion/exclusion criteria, 267 consecutive patients were finally included in this study. The median age was 58 (27–85) years. Of the 267 cases, 255 were squamous carcinoma (SCC) and 12 were non-SCC (NSCC; adenocarcinomas or adenosquamous carcinoma).

Tumor classification by FIGO clinical stage showed stage IIB in 100 patients (37.4%), stage Ⅲ in 161 patients (17 for ⅢA, 104 for ⅢB, 40 for IIIC), and stage IVA in 6 patients (2.2%). Almost half of the tumors (53 patients, 43.8%) showed aggressive histology (poorly). Based on ^{18}F-FDG PET/CT, 97 patients had no lymph node metastases, whereas 170 (64.0%) patients had lymph node metastases, among whom 43 (25.3%) had both pelvic and a PALN metastasis.

Testing for serum tumor markers showed SCC antigen (SCC-Ag)-positive (≥ 10.40 ng/mL) status in 128 patients (47.9%). A high level of carcinoembryonic antigen (CEA) (≥ 7.11 ng/mL) was present in 58 patients (21.70%).

All 267 patients completed radical radiotherapy, with 21.7% receiving lombo-aortic EBRT. Most patients (94.4%) underwent high-dose-rate brachytherapy. The primary therapy was concurrent CRT for 210 patients (78.7%), and the remaining 57 patients (21.3%) received radiotherapy alone.

Disease progression prediction

The median follow-up time was 36.52 (3.09–61.29) months. At the end of follow-up, 31 patients (11.6%) had died and 49 patients (18.4%) progressed as a result of related disease

Table 1 Clinicopathological characteristics

Variable	*N* (%)
Age (year)	267
Median (range)	58(27–85)
Classification	267
SCC	255(95.5%)
NSCC	12(4.5%)
Histologic grade	121
Well	5(4.1%)
Moderate	63(52.1%)
Poorly	53(43.8%)
FIGO stage	267
IIB	100(37.4%)
IIIA	17(6.4%)
IIIB	104(39.0%)
IIIC	40(15.0%)
IVA	6(2.2%)
LN metastasis	267
No	97(36.0%)
Yes	170(64.0%)
PALN metastasis	267
No	224(83.9%)
Yes	43(16.1%)
Lombo-aortic EBRT	267
Yes	58(21.7%)
No	209(78.3%)
BT	267
Yes	252(94.4%)
No	15(5.6%)
Concurrent CRT	267
Yes	210(78.7%)
No	57(21.3)

SCC squamous cell carcinoma, *PALN* para-aortic lymph node, *EBRT* external beam radiation therapy, *BT* brachytherapy, *CRT* chemoradiotherapy

during follow-up. Conversely, 187 patients remained in remission with no evidence of disease recurrence. The 3-year PFS was 51.3%.

We analyzed the PET/CT images of patients with LACC and acquired the specific values of SUV_{max}, MTV, and TLG of the primary lesion or positive lymph nodes to predicting the PFS, considering the sensitivity and specificity for progression (Figure S1). Patient outcomes were in comparison according to the quantitative metabolic parameters of PET in Table 2. The optimal cut-off values of pSUVmax, pMTV, and pTLG were 13.70, 29.39 cm^3, and 259.05, respectively. Of these metabolic parameters, only pMTV and pTLG were significantly associated with the disease progression ($p=0.001$ and $p=0.013$, respectively). The sensitivities and specificities of MTV were 52.5% and 69.0%, respectively, and those of TLG were 46.2% and 70.1%, respectively. For patients with lymph node metastases, $nSUV_{max}$ and nTLG were significantly associated with recurrence. The best cut-off values for $nSUV_{max}$ and nTLG were 5.29 and 18.66, respectively. The sMTV and sTLG also showed a significant relationship with disease progression, with cut-off values of 30.25 cm^3 and 229.62, respectively. The $pSUV_{max}$ and nMTV were not significant predictors of outcome in this analysis.

Based on the optimal threshold, PET parameters were dichotomized to generate Kaplan–Meier survival plots (Fig. 2). The PFS differed significantly between patients with high versus low MTV or TLG values based on the log-rank test. The 3-year PFS for patients with high versus low pMTV and pTLG values were 44.6% and 41.5% versus 55.4% and 56.6%, respectively ($p=0.001$; $p=0.006$). The prognostic impact of pretreatment PET with regard to 3-year PFS remained significant between the high $nSUV_{max}$ and low $nSUV_{max}$ groups at 42.2% and 56.3%, respectively ($p=0.001$). For patients with nTLG ≥ 18.66, the 3-year PFS was significantly lower than that of those with nTLG < 18.66 (40.0% vs. 53.1%, $p=0.09$). Patients with low sMTV and sTLG values had median PFS of 37.25 (3.09–61.29) months and 38.04 (3.09–61.29) months, respectively, whereas patients with high sMTV and sTLG values had median PFS of 32.93 (3.72–60.86) months and 32.59 (3.72–60.86) months respectively; this difference was statistically significant ($p=0.001$; $p=0.001$).

Univariate and multivariate analyses for PFS

Univariate and multivariate analyses were conducted to compare the prognostic value of histologic prognostic factors and metabolic parameters (Table 3). In univariate analysis, FIGO staging IIIA–IVA, lack of concurrent CRT experience, CEA ≥ 7.11 ng/mL, SCC-Ag ≥ 10.40 ng/mL, pMTV ≥ 29.39 cm^3, pTLG ≥ 259.05, $nSUV_{max}$ ≥ 5.29, nTLG ≥ 18.66, sMTV ≥ 30.25 cm^3, and sTLG ≥ 229.62 were significant predictors of poor PFS ($p<0.05$). Multivariate Cox regression analysis was performed to further investigate the prognostic value of all the factors just described. Results showed that concurrent CRT (HR 0.44; 95% CI 0.23–0.84; $p=0.014$), CEA ≥ 7.11 ng/mL (HR 2.30; 95% CI 1.24–4.24; $p=0.008$), and $nSUV_{max}$ ≥ 5.29 (HR 2.46; 95% CI 1.29–4.70; $p=0.006$) were independent prognostic factors for PFS (Fig. 3), whereas FIGO stage, serum SCC-Ag level, pMTV, pTLG, nTLG, sMTV, and sTLG were not independent predictors for recurrence.

Discussion

Our study aimed to explore the predictive value of PET/CT parameters and several clinicopathological features in patients with LACC for disease progression. Results

Table 2 Patient clinicopathologic parameters and PET-CT parameters according to progression status

Characteristics	All patients ($N=267$)	Progression ($N=80$)	Progress rate (%)	Non-progression ($N=187$)	χ^2	p value
Age (year)						0.077
Median (range)	58(27–85)	61(27–85)		57(30–79)		
Classification					2.404	0.121
SCC	255	74	29.0	181		
NSCC	12	6	50.0	6		
Histologic grade					0.933	0.334
Well and moderately	68	20	29.4	48		
Poorly	53	20	37.7	33		
FIGO stage					4.830	0.028*
IIB	100	22	22.0	78		
IIIA-IVA	167	58	34.7	109		
LN metastasis					1.321	0.250
No	97	33	34.0	64		
Yes	170	47	27.6	123		
PALN metastasis					0.165	0.685
No	224	66	29.5	158		
Yes	43	14	32.6	29		
Number of metastatic LN					2.205	0.138
<6	227	64	28.2	163		
≥ 6	40	16	40.0	24		
Lombo-aortic EBRT					0.721	0.396
No	209	60	28.7	149		
Yes	58	20	34.5	38		
BT					2.113	0.146
No	15	7	46.7	8		
Yes	252	73	29.0	179		
Concurrent CRT					10.463	0.001*
No	57	27	47.4	30		
Yes	210	53	25.2	157		
CEA					9.717	0.020*
≥ 7.11 ng/ml	58	27	46.6	31		
<7.11 ng/ml	209	53	25.4	156		
SCC-Ag					9.702	0.002*
≥ 10.40 ng/ml	128	50	39.1	78		
<10.40 ng/ml	139	30	21.6	109		
$pSUV_{max}$					2.559	0.110
<13.70	104	37	35.6	67		
≥ 13.70	163	43	26.4	120		
pMTV					10.456	0.001*
<29.39 cm^3	166	38	22.9	128		
≥ 29.39 cm^3	101	42	41.6	59		
pTLG					6.107	0.013*
< 259.05	173	43	24.9	130		
≥ 259.05	94	37	39.4	57		
$nSUV_{max}$					9.812	0.002*
<5.29	80	13	16.3	67		
≥ 5.29	90	34	37.8	56		
nMTV					3.771	0.052
<5.08 cm^3	110	25	22.7	85		

Table 2 (continued)

Characteristics	All patients ($N=267$)	Progression ($N=80$)	Progress rate (%)	Non-progression ($N=187$)	χ^2	p value
≥ 5.08 cm^3	60	22	36.7	38		
nTLG					6.202	0.013*
<18.66	115	25	21.7	90		
≥ 18.66	55	22	40.0	33		
sMTV					9.183	0.002*
<30.25 cm^3	151	34	22.5	117		
≥ 30.25 cm^3	116	46	39.7	70		
sTLG					7.521	0.006*
<229.62	154	36	23.5	118		
≥ 229.62	113	44	38.9	69		

SCC squamous cell carcinoma, *PALN* para-aortic lymph node, *EBRT* external beam radiation therapy, *BT* brachytherapy, *CRT* chemoradiotherapy, *pSUV$_{max}$* primary tumor maximum standardized uptake values, *pMTV* primary tumor metabolic tumor volume, *pTLG* primary tumor total lesion glycolysis, *nSUV$_{max}$* SUV$_{max}$ of lymph nodes, *nMTV* MTV of all positive lymph nodes, *nTLG* TLG of all positive lymph nodes, *sMTV* the sum of pMTV and nMTV, *sTLG* the sum of pTLG and nTLG

*Represents $p<0.05$ for comparison between indicator groups

showed that the SUV$_{max}$ value of metastatic lymph nodes, serum CEA level, and concurrent CRT treatment may independently predict PFS in this population. The use of PET/CT combined with other clinicopathological characteristics provides a more comprehensive understanding of patient information and guidance for clinicians on formulating treatment plans.

Locally advanced cervical cancer remains a disease with a high rate of recurrence, and many patients undergo treatments that may not be beneficial. ^{18}F-FDG PET/CT has been recognized as a useful diagnostic technique in clinical oncology. Previously an association between the intensity of FDG uptake at the cervical tumor and poor outcomes has been documented [10, 14]. Burcak et al. [15] supported that SUV$_{max}$ which represents the metabolic activity of the most aggressive cells in malignant lesions, is an independent prognostic factor for disease-control survival of LACC.

Nevertheless, primary tumor SUV$_{max}$ was insufficient as a reliable prognostic indicator in most studies, according to a meta-analysis [8]. Similarly, our study showed no correlation between pSUV$_{max}$ and PFS in LACC. This finding may be attributed to the heterogeneity in tumor tissue, which cannot be fully reflected by SUV$_{max}$ within the selected region. However, SUV$_{max}$ of metastatic lymph nodes was significantly associated with PFS in our cohort.

Laurie et al. [16] reported that high SUV$_{max}$ in metastatic lymph nodes was a significantly poor prognostic factor of extracervical recurrence-free survival. Won et al. [17] also suggested that SUV$_{max}$ of metastatic lymph nodes as a continuous variable was a critical predictive index for disease-free survival and OS. We suspect that the high FDG uptake of cancer cells in the lymph nodes is more indicative of their high degree of invasiveness and biological activity, which leads to recurrence and poor prognosis.

Volume-based parameters, such as MTV or TLG, take into consideration both tumor volume and metabolic activity as crucial parameters of prognosis and treatment response, thus making them better prognostic factors than SUV$_{max}$. Cem et al. [18] highlighted that cervical MTV and TLG from pretreatment PET/CT were useful for predicting patient OS or PFS after chemoradiotherapy for patients with LACC. Likewise, Paulina et al. [19] demonstrated that cervical MTV was a critical prognostic factor for OS, event-free survival, locoregional control and freedom from distant metastases and should be used to guide oncologists in selecting individualized therapies. Deng et al. [20] and Paulina et al. [21] reported that total MTV was a significant predictor of recurrence and overall survival of LACC in both univariate analysis and multivariate analysis. Liang et al. [22] also proposed that total TLG measured by ^{18}F-FDG PET/CT was obviously correlated with survival outcomes in patients with LACC. However, other studies took the opposite view and reported that further confirmation was required regarding the role of MTV and TLG to predict the prognosis of patients with cervical cancer and to develop treatment strategies [23, 24]. In our study, pMTV ≥ 29.39 cm^3 (HR 2.13; 95% CI 1.37–3.31; $p=0.001$), pTLG ≥ 259.05 (HR 1.84; 95% CI 1.19–2.86; $p=0.006$), nTLG ≥ 18.66 (HR 2.11; 95% CI 1.19–3.74; $p=0.009$), sMTV ≥ 30.25 cm^3 (HR 2.08; 95% CI 1.33–3.24; $p=0.001$), sTLG ≥ 229.62 (HR 2.01; 95% CI 1.30–3.13; $p=0.001$) were significantly poor prognostic factors of PFS in univariate analysis. However, statistically significant associations were not found between these parameters and disease progression in multivariate analysis. We considered that the reasons for these different results may

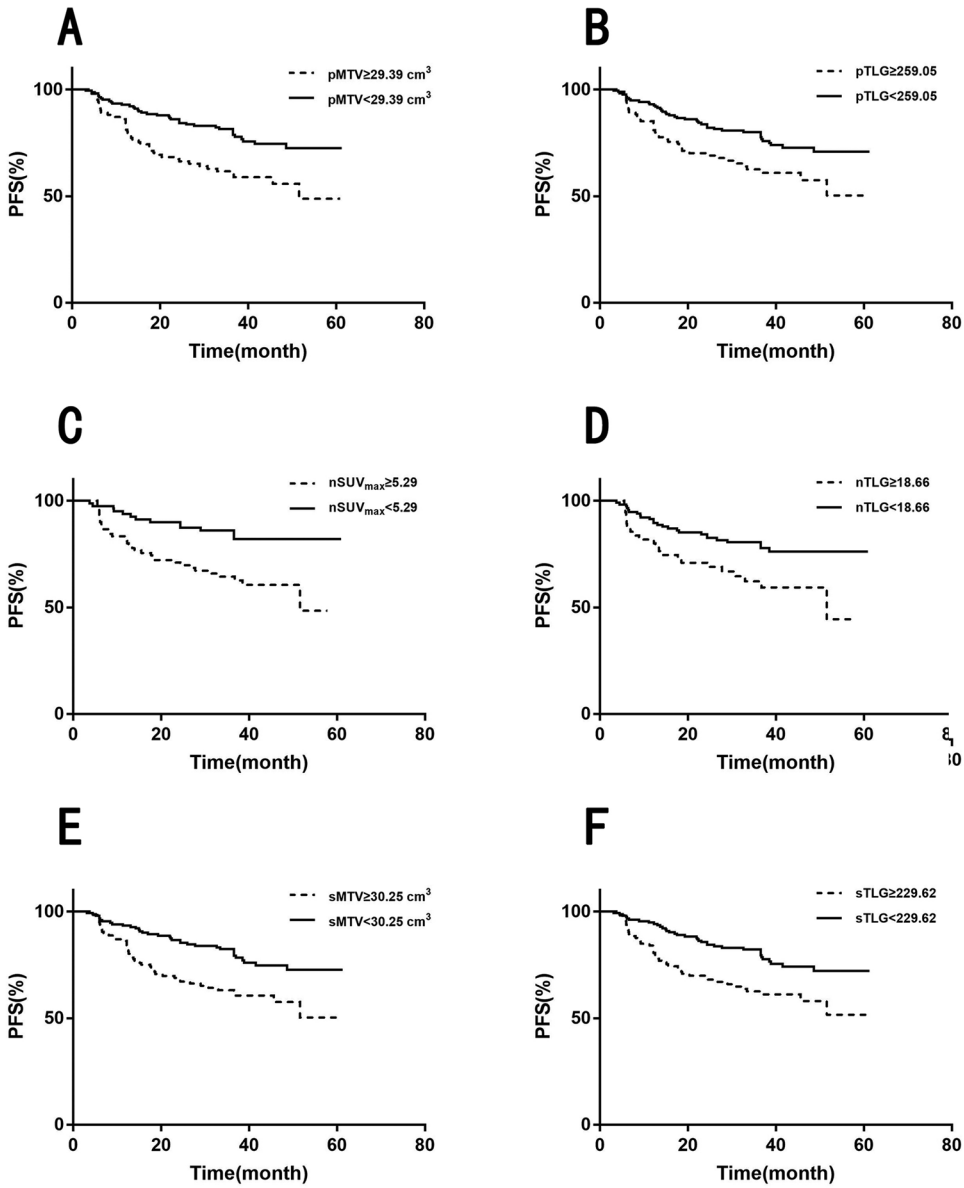

Fig. 2 Kaplan–Meier survival curves of PET parameters for PFS in 267 patients with LACC

be related to the inconsistency in the definition of MTV in different studies. In addition, several study limitations may cause differences in results, such as publication bias, the small sample size of each enrolled study, and inconsistent treatment methods among different medical centers.

Several traditional clinical and pathological factors are identified as poor prognostic factors, including FIGO stage, lymph node metastasis, parametrial invasion and histological tumor type [25–27]. Cervical cancer contains two major histopathological types: SCC (75% of cases) and NSCC, and these two types differ in their cellularity and proliferation potential. Because of different tissue integrity and proliferation potential, SCC and NSCC may have different manifestations of the tumor metabolic burden and cell metabolic activity on PET/CT scanning [28]. Most patients in our cohort had SCC—a study characteristic that to some extent may avoid bias caused by heterogeneity of the histological subtype. In our study, high FIGO stage was associated with adverse prognosis, as indicated by Kaplan–Meier survival plots. Present of metastatic PALN was observed to have no correlation with PFS, which may be in part due to a small number of patients (16.1%) having PALN metastasis and all of these patients having undergone lombo-aortic EBRT. Meanwhile, when interpreting PET/CT results, we focused both on lymph nodes and the primary tumor and explored their role in turn. Our study indicated that $nSUV_{max}$ may help identify patients at the onset of treatment who are at increased risk for relapse and death, with a threshold of 5.29.

Our study also identified serum tumor markers and radiotherapy methods for cervical cancer that may provide

Table 3 Univariate and multivariate analyses of PFS

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (< 66 vs. ≥ 66 years)	1.49 (0.95–2.34)	0.080		
Classification (SCC vs. NSCC)	1.89 (0.82–4.36)	0.126		
Histologic grade (well and moderately vs. poorly)	0.75 (0.40–1.39)	0.349		
FIGO stage (IIB vs. IIIA-IVA)	1.88 (1.15–3.07)	0.011*	1.24 (0.63–2.44)	0.532
LN metastasis (no vs. yes)	0.85 (0.54–1.32)	0.462		
PALN metastasis (no vs. yes)	1.29 (0.72–2.29)	0.391		
Number of metastatic LN (< 6 vs. ≥ 6)	1.59 (0.92–2.75)	0.095		
Lombo-aortic EBRT (no vs. yes)	1.45 (0.87–2.41)	0.150		
BT (no vs. yes)	0.50 (0.23–1.08)	0.072		
Concurrent CRT (no vs. yes)	0.49 (0.31–0.78)	0.002*	0.44 (0.23–0.84)	0.014*
CEA (≥ 7.11 ng/ml vs. < 7.11 ng/ml)	2.03 (1.27–3.22)	0.002*	2.30 (1.24–4.25)	0.008*
SCC-Ag (≥ 10.40 ng/ml vs. < 10.40 ng/ml)	2.05 (1.30–3.23)	0.001*		
$pSUV_{max}$ (< 13.70 vs. ≥ 13.70)	0.80 (0.51–1.24)	0.314		
pMTV (< 29.39 cm^3vs. ≥ 29.39 cm^3)	2.13 (1.37–3.31)	0.001*	2.40 (0.60–9.64)	0.218
pTLG (< 259.05 vs. ≥ 259.05)	1.84 (1.19–2.86)	0.006*	0.66 (0.21–2.09)	0.482
$nSUV_{max}$ (< 5.29 vs. ≥ 5.29)	2.76 (1.46–5.24)	0.001*	2.46 (1.29–4.70)	0.006*
nMTV (< 5.08 cm^3 vs. ≥ 5.08 cm^3)	1.75 (0.99–3.10)	0.053		
nTLG (< 18.66 vs. ≥ 18.66)	2.11 (1.19–3.74)	0.009*	1.30 (0.64–2.65)	0.471
sMTV (< 30.25 cm^3 vs. ≥ 30.25 cm^3)	2.08 (1.33–3.24)	0.001*	0.59 (0.14–2.55)	0.479
sTLG (< 229.62 vs. ≥ 229.62)	2.01 (1.30–3.13)	0.001*	1.93 (0.56–6.68)	0.301

PFS progression-free survival, *SCC* squamous cell carcinoma, *PALN* para-aortic lymph node, *EBRT* external beam radiation therapy, *BT* brachytherapy, *CRT* chemoradiotherapy, $pSUV_{max}$ primary tumor maximum standardized uptake values, *pMTV* primary tumor metabolic tumor volume, *pTLG* primary tumor total lesion glycolysis, $nSUV_{max}$ SUV_{max} of lymph nodes, *nMTV* MTV of all positive lymph nodes, *nTLG* TLG of all positive lymph nodes, *sMTV* the sum of pMTV and nMTV, *sTLG* the sum of pTLG and nTLG, *HR* hazard ratio, *95% CI* 95% confidence interval

*Represents $p < 0.05$ for comparison between indicator groups

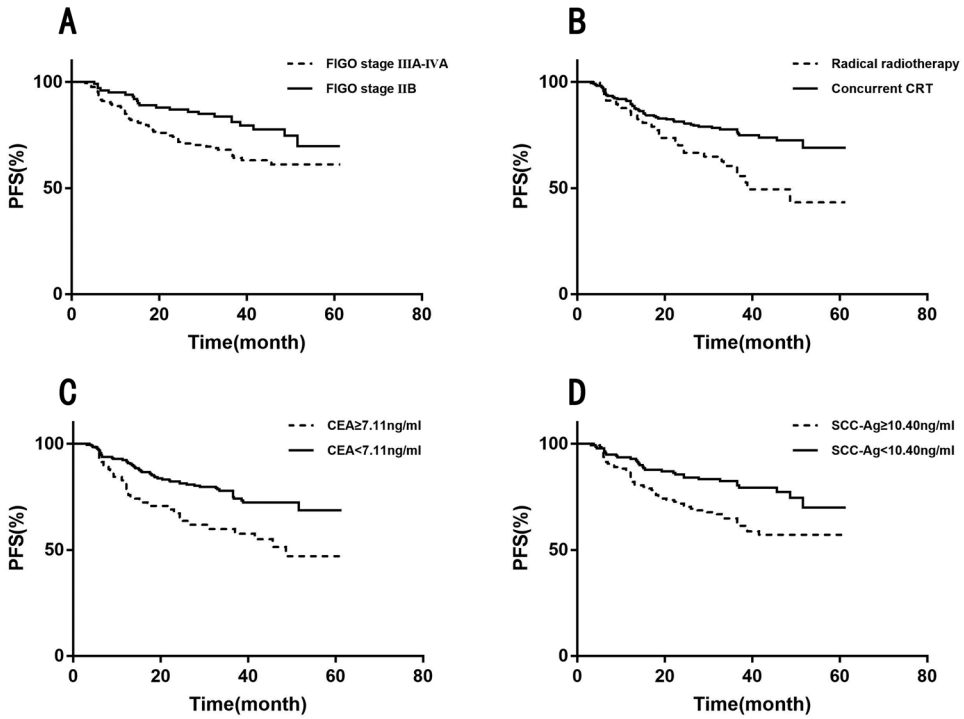

Fig. 3 Kaplan–Meier survival curves of clinicopathological indicators for PFS in 267 patients with LACC

patient prognostic information. Results demonstrated that patients with treatment failure showed significantly higher levels of CEA or SCC-Ag than the those with long-term outcomes. The risk of recurrence was significantly increased in patients with LACC treated with radical radiotherapy alone compared with those treated with standard concurrent chemoradiotherapy and brachytherapy. These findings were consistent with those of previous research [29, 30].

Our study is unique because it includes a large number of participants (267 patients) with LACC at different disease stages, and it reviewed 12 clinicopathological indicators and 8 metabolic parameters involving metastatic lymph node information and the whole body tumor metabolic burden to explore their prognostic significance. Despite these strengths, our study has some notable limitations. First, it was a single-center study with a retrospective design, which may have biased prognostication; therefore, a prospective study in a larger cohort is necessary. Moreover, positive lymph nodes in our study were identified on PET/CT and not by histopathologic verification. In addition, aligned with the time of case inclusion, the 2014 FIGO staging classifications were used, which differ somewhat from the current new 2018 FIGO staging. Finally, combined with recent promising methods in clinical oncology, such as radiomics, PET/magnetic resonance imaging, and new imaging agents, use of 18F-FDG/PET and the clinicopathological indicators and metabolic parameters addressed in this study may yield more significant predictive values for the prognosis of cervical cancer.

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Author contributions WQP mainly took charge of quality control of PET imaging. JLS, the first author, collected, analyzed and interpreted PET data; drafted the manuscript. HQY, JFJ and XMY collected clinical data and followed-up LACC patients. LFL, the corresponding author, responsible for the designing of the study and obtaining grants and funding to support the trial; revised the manuscript and enhanced the intellectual content of the manuscript. All authors read and approved the final manuscript.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB number: IRB-2022-423) of Zhejiang Cancer Hospital approved this study.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the images in Figs. 1, 2, 3.

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