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FULL PAPER

Pretreatment metabolic tumour volume and total lesion glycolysis are not independent prognosticators for locally advanced cervical cancer patients treated with chemoradiotherapy

[1]OZAN CEM GULER, MD, [2]NESE TORUN, MD, [3]BERNA AKKUS YILDIRIM, MD and [3]CEM ONAL, MD

[1]Department of Radiation Oncology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey
[2]Department of Nuclear Medicine, Baskent University Faculty of Medicine, Adana, Turkey
[3]Department of Radiation Oncology, Baskent University Faculty of Medicine, Adana, Turkey

Address correspondence to: Mr Ozan Cem Guler
E-mail: *ocguler@gmail.com*

Objective: To evaluate the prognostic significance of metabolic parameters derived from fludeoxyglucose (FDG) positron emission tomography (PET)/CT, in cervical cancer patients treated with concurrent chemoradiotherapy.
Methods: We retrospectively reviewed medical records from 129 biopsy-proven non-metastatic cervical cancer patients treated with external radiotherapy and intracavitary brachytherapy at our department. Correlation between metabolic parameters and tumour characteristics was evaluated. Prognostic factors for survival, local control and distant metastasis were analysed.
Results: The median follow up for all patients and surviving patients was 30.0 months (range, 3.7–94.7 months) and 50.5 months (range, 14.5–94.7 months), respectively. The 2- and 5-year overall survival (OS) and disease-free survival (DFS) rates were 68 42, 54 and 38%, respectively. The maximum standardized uptake value (SUV_{max}), SUV_{mean}, metabolic tumour volume (MTV) and total lesion glycolysis were significantly higher in patients with larger tumours (>4 cm) and partial regression or progressive disease after definitive treatment compared to patients with smaller tumour (≤4 cm) and post-treatment complete response. On univariate analysis, stage, lymph node metastasis, tumour size >4 cm, SUV_{max}, MTV, SUV_{mean} and total lesion glycolysis were prognostic factors for OS and DFS. On multivariate analysis, only larger tumour and presence of lymph node metastasis were significant prognostic factors for both OS and DFS. Additionally, extensive stage was a significant prognosticator for DFS.
Conclusion: Although, metabolic parameters derived from FDG-PET/CT had a prognostic significance in univariate analysis, the significance was lost in multivariate analysis where tumour stage, size and lymph node status were the only independent parameters.
Advances in knowledge: The clinical benefit of using FDG-PET/CT metabolic parameters to evaluate the high-risk patients among cervical cancer patients and to eventually change patient management still needs further clarification.

INTRODUCTION

Cervical cancer is the most frequent gynaecological cancer worldwide.[1] Age, initial stage and lymph node status are the most commonly used prognostic factors associated with clinical outcome.[2] Nearly half of the patients present with advanced disease.[3] Approximately 30–40% of patients with locally advanced cervical cancer will eventually have tumour recurrence.[3] Therefore, additional efforts are required to predict the prognostic factors for these high-risk patients. The International Federation of Gynecology and Obstetrics[4] staging is based on clinical findings. The optimal treatment decision requires accurate staging, and the evaluation of lymph node involvement and primary tumour extension are also quite important. CT, MRI and ^{18}F-fludeoxyglucose (FDG) positron emission tomography (PET)/CT are the most commonly used imaging modalities.

Nowadays, FDG-PET/CT has become an important component of staging in patients with cervical cancer.[5–12] Its ability to identify lymph node involvement, distant disease and recurrences, and assess treatment response has been shown in various studies.[9,13,14] Also, some studies inferred the relationship between FDG uptake and outcome in cervical cancer patients.[10,11,13] The semi-quantitative parameter

derived from FDG-PET, which is the maximum standardized uptake value (SUV_{max}) of the primary tumour, is known to be a significant prognostic factor in cervical cancer patients.[6,11,15] However, SUV_{max} is measured on a single voxel and may not represent the metabolic activity of the whole tumour. Recently, other metabolic parameters derived from FDG-PET, such as average SUV (SUV_{mean}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG), have been investigated in cervical cancer patients.[16–23] Data on the effectiveness of MTV and/or TLG in cervical cancer are scarce and mainly based on surgical series with early stage tumour.[23–25] Only a few studies evaluated the prognostic significance of MTV and TLG in locally advanced cervical cancer treated with definitive chemoradiotherapy (ChRT), but with limited patient numbers.[23,26–28] It is still under debate which metabolic parameter derived from FDG-PET is more reliable in predicting prognosis in locally advanced cervical cancer patients treated with definitive ChRT.

Since there is limited experience in volume-based parameters derived from FDG-PET in locally advanced cervical cancer patients treated with definitive ChRT, we sought to evaluate the prognostic significance of MTV and TLG, which are metabolic parameters measured by ^{18}F-FDG-PET/CT, in locally advanced cervical cancer patients treated with concurrent ChRT.

METHODS AND MATERIALS

Patients

The medical records of 129 eligible patients with biopsy-proven cervical cancer treated with definitive ChRT with a curative intent between February 2007 and March 2014 at Baskent University were retrospectively reviewed. Approval was obtained from the institutional review board for this retrospective outcome analysis.

All patients underwent routine clinical staging, including recording of medical history reviews, physical and gynaecological examinations, complete blood count, blood chemistry tests and MRI or CT of the abdomen and pelvis where appropriate. The patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. All patients also underwent FDG-PET/CT for initial diagnosis, staging and radiotherapy (RT) planning.

PET/CT technique

The patients were imaged using a dedicated PET/CT system (Discovery-STE 8; General Electric Medical Systems, Milwaukee, WI) as previously described.[29] Briefly, the patients fasted for at least 6 h before intravenous administration of 370 to 555 MBq (10–15 mCi) FDG. Pre-injection blood glucose levels were measured to make sure that they were below 150 mg dl^{-1}. During the distribution phase, the patients laid supine in a quiet room. Combined image acquisition began 60 min after FDG injection. The patients were scanned on a flat-panel, carbon-fibre composite table insert. First, an unenhanced CT scan (5 mm slice thickness) from the base of the skull to the inferior border of the pelvis was acquired using a standardized protocol (140 kV and 80 mA). The subsequent PET scan was acquired in three-dimensional (3D) mode from the base of the skull to the inferior border of the pelvis (sixseven to bed positions, 3 min per position) without repositioning the patient on the table. CT and PET images were acquired with the patient breathing shallowly. Attenuation was corrected using the CT images. Areas of FDG uptake were categorized as malignant based on location, intensity, shape, size and visual correlation with CT images to differentiate physiological uptake from pathological uptake. A lymph node was considered PET-positive, if its FDG uptake was greater than blood pool activity or surrounding background tissues, depending on the size of the node.

Figure 1. Measurement of MTV using a SUV-based automated contouring program. (a) The contour around the target lesions inside the boundaries was automatically produced and the voxels presenting SUV intensity >2.5 within the contouring margin were incorporated to define the tumour volumes (black line). (b) The boundaries between bladder (arrow) is checked manually in order to minimize misinterpretation. MTV, metabolic tumour volume; SUV, standardized uptake value.

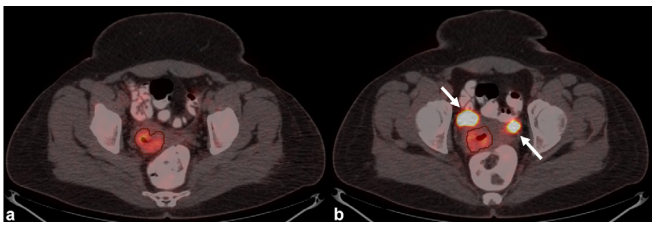


Image analysis

The tumour size is the maximum diameter measured on PET-CT images. For each FDG-PET/CT study, the SUV_{max}, SUV_{mean}, MTV and TLG values of the primary tumour were measured. The SUV value greater than 2.5 was considered positive. A volumetric region of interest (ROI) around the outline of primary tumour was placed on the axial PET/CT images using the semi-automatic software. The ROI borders were manually adjusted by visual inspection of the primary tumour for avoiding an overlap on adjacent FDG-avid structures. Furthermore, the activity in the urinary tract is excluded. The MTV was defined as the regions equal to or greater than SUV of 2.5[25,26] (Figure 1). To prevent the inclusion of adjacent normal structures such as the bladder, lymph nodes and the bowel, the tumour region was expanded from a single-seed voxel within the tumour via the region-growing morphologic operation. The PET parameters including SUV_{mean}, MTV and the SUV_{max} were automatically acquired with automatically generated ROI of the primary tumour. The TLG was calculated by multiplying SUV_{mean} and MTV.

Treatment

Patients were treated with a combination of 3D conformal external beam RT with concurrent weekly 40 mg m^{-2} cisplatin and high-dose-rate brachytherapy (BRT) as previously described.[30] Briefly, a total of 50.4 Gy external RT (1.8 Gy per fraction, daily, Monday through Friday) was delivered using 18 MV photons. The para-aortic region was also included in patients with FDG uptake in para-aortic lymph nodes. Para-aortic fields were treated with 45 Gy in 1.8-Gy fraction doses. In patients with enlarged lymph nodes, an additional 9-Gy boost dose was given.

3D brachytherapy planning was performed using 7 Gy per fraction prescribed to the target minimum, given in four fractions after completion of external beam RT.

Clinical follow up

Clinical follow up of patients was performed every 3 months for 2 years, then every 6 months up to 5 years and annually, thereafter. Biopsy was not performed before 6 months of the completion of ChRT. Failure was defined as biopsy-proven recurrence or documented progression of disease in serial-imaging studies. Failure patterns were determined by follow up imaging studies and were divided into five groups: none, isolated local failure (central pelvis), locoregional failure (pelvic lymph nodes), distant failure (including para-aortic and supraclavicular lymph nodes) and combined local/locoregional plus distant failure.

Statistical analysis

All statistical analyses relied on standard software [SPSS v. 20; SPSS Inc. (IBM), Chicago, IL]. The time to event was calculated as the time interval from the date of diagnosis to the date of first finding on clinical or imaging examination that suggested disease recurrence. Pelvic disease recurrence was defined as disease in the cervical tumour, pelvic lymph nodes, or both. All time-related events (failure or death) were calculated from the last day of RT to the last follow up or death. Disease-free survival (DFS) and overall survival (OS) rates were calculated using the Kaplan–Meier method. Correlations between parameters were calculated using the Pearson test. Variables shown to be significant or borderline significance ($p < 0.1$) were also selected for multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards model, using covariates with a p-value less than 0.10 based on univariate analysis. Same results were observed after forward and backward inclusion in multivariate analysis. Receiver operating characteristic curves were generated for the SUV_{max}, SUV_{mean}, MTV and TLG values to determine the cut-off values for predicting recurrence and survival that yielded optimal sensitivity and specificity. Clinicopathological factors and follow up data from our cervical cancer database were analysed for correlations with SUV_{max}, SUV_{mean}, MTV and TLG. All p-values ≤ 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Patient and tumour characteristics are presented in Table 1. More than 80% of the patients had International Federation of Gynecology and Obstetrics Stage IIB or higher disease, and most patients had squamous cell carcinoma. Cisplatin was the only chemotherapeutic agent used during RT. All patients were treated with concurrent chemotherapy except 16 (12%) of them. Among the patients receiving concurrent chemotherapy: 109 patients (97%) received 6 cycles, 3 patients (2%) received 3 cycles and 1 patient (1%) received 2 cycles of chemotherapy during RT. External beam RT was administered in median 1.8 Gy (range, 1.8–2 Gy) at daily fractions to a median total dose of 50.4 Gy (range, 45–55.8 Gy). BRT was administered to a median total dose of 28 Gy (range, 21–28 Gy) at 7 Gy fractions. 77 patients (60%) were treated with 3D-conformal BRT while 52 patients (40%) were treated with 2D BRT.

Table 1. Patient and tumour characteristics

Characteristics	Number of patients	Percentage (%)
Age, median (range), years	57 (22–83)	
Tumour size (mean ± SD), cm	5.6 ± 1.9	
Stage		
IB2	16	13
IIA	4	3
IIB	52	40
IIIA	13	10
IIIB	36	28
IVA	8	6
Pathology		
SCC	119	92
Adenocarcinoma	10	8
Lymph node metastasis		
None	53	41
Pelvic	53	42
Pelvic + para-aortic	22	17

SCC, squamous cell carcinoma; SD, standard deviation.

Treatment outcomes

The median follow up for all patients and surviving patients was 30.0 months (range, 3.7–94.7 months) and 50.5 months (range, 14.5–94.7 months), respectively. Of the 129 patients in the study cohort, 71 (55%) developed local, locoregional, distant failure or combination of local/locoregional and distant failures. Of these, 26 (20%) developed distant metastases, 23 (18%) had local recurrence, 12 (9%) had locoregional recurrence and 10 (8%) developed both local/locoregional and distant failure.

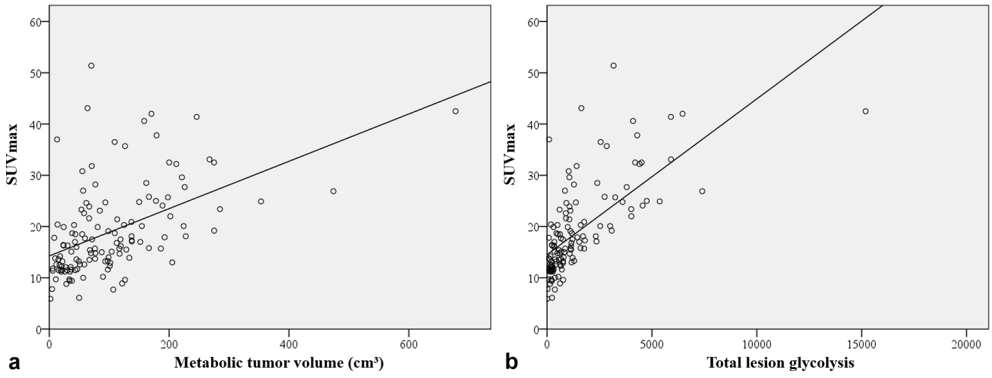
At the time of the last follow up, 54 patients (42%) were alive [3 (2%) with disease], and 75 patients (58%) were dead. Of these latter patients, 68 (52%) died due to disease and 7 (5%) died from other causes.

The treatment response was evaluated in 89 patients (69%) with FDG-PET/CT delivered median 3.2 months (range 2.9–4.6 months) after completion of definitive ChRT. Of those, 66 patients (74%) had complete metabolic response, 18 patients (20%) had partial response and 5 patients (6%) had progressive disease (PD).

FDG-PET/CT findings

The mean ± SD SUV_{max}, SUV_{mean}, MTV and TLG were 19.0 ± 8.9 (range, 5.9–51.4), 12.0 ± 6.5 (range, 3.5–45.2), 102.2 ± 76.5 cm^3 (range, 1.9–677.9 cm^3) and 1467.8 ± 771.3 (range, 8.1–15, 185.4) for the entire group, respectively. There was a weak correlation between SUV_{max} of primary cervical tumours and MTV [Pearson correlation coefficient (r)=0.245; $p < 0.001$] (Figure 2a). Additionally SUV_{max} of primary cervical tumours and TLG were significantly correlated ($r = 0.456$; $p < 0.001$) (Figure 2b).

Figure 2. Regression plots of (a) the SUV_{max} of primary cervical tumours *vs* metabolic tumour volume (r = 0.245; p < 0.001) and (b) SUV_{max} of primary cervical tumours *vs* total lesion glycolysis (r = 0.456; p < 0.001). SUV, standardized uptake value.

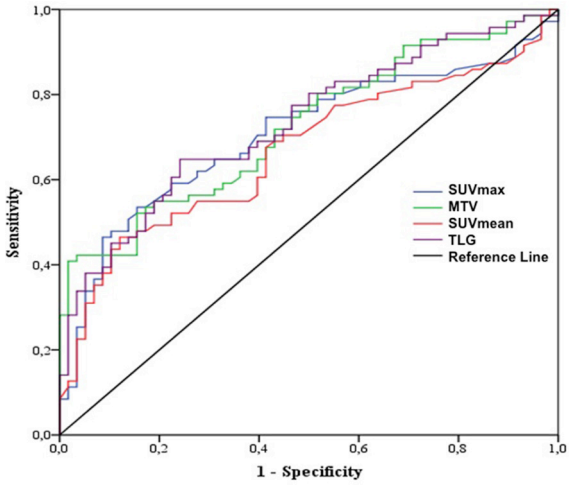


A weak correlation between tumour size and SUV_{max} (r = 0.182; p < 0.001), and moderate correlations between tumour size and MTV (r = 0.461; p < 0.001), and TLG (r = 0.419; p < 0.001) were observed. In receiver operating characteristics curve analysis, the area under curve (AUC) and determined cut-off values for SUV_{max}, SUV_{mean}, MTV and TLG were 0.706 [p < 0.001; 95% confidence interval (CI) (0.615–0.796)] and 16.4, 0.666 [p = 0.001; 95% CI (0.573–0.760)] and 10.0, 0.723 (p < 0.001; 95% CI (0.637–0.809)] and 73.8 cm^3, 0.731 [p < 0.001; 95% CI 0.646–0.817)] and 760.5, respectively (Figure 3).

Correlations between FDG-PET parameters and patient/tumour characteristics

The SUV_{max}, SUV_{mean}, MTV and TLG were significantly higher in patients with larger tumours (>4 cm) and partial regression or progressive disease after definitive treatment compared to patients with smaller tumour (≤4 cm) and post-treatment complete response (Table 2). Additionally, patients with adenocarcinoma had significantly higher SUV_{mean} compared to patients with squamous cell carcinoma.

Figure 3. Receiver operating characteristics curves in predicting tumour recurrence according to SUV_{max}, SUV_{mean}, MTV and TLG. MTV, metabolic tumour volume; SUV_{max}, maximum standardized uptake value; SUV_{mean}, average standardized uptake value; TLG, total lesion glycolysis.



Survival analysis and prognostic factors

The 2- and 5-year OS and DFS rates were 68 and 42%, 54 and 38%, respectively (Figure 4a,b). On univariate analysis, stage, lymph node metastasis, tumour size >4 cm, SUV_{max}, MTV, SUV_{mean} and TLG were prognostic factors for OS and DFS.

The OS and DFS rates were significantly lower in patients with SUV_{max} of <16.4 compared to those with SUV_{max} ≥16.4 (p = 0.003 and p = 0.001, respectively) (Figure 5a,e). Patients with a SUV_{mean} of <10.0 had better DFS rates compared to those with SUV_{mean} ≥10.0 or greater (p = 0.04) (Figure 5g). However, there is no significant difference in OS according to SUV_{mean} values (Figure 5c). The OS and DFS rates were significantly lower in the patients with a MTV of <73.8 cm^3 compared to those with a MTV ≥ 73.8 cm^3 (p = 0.004 and p = 0.003, respectively) (Figure 5b,f). Also, significantly better OS and DFS rates were observed in patients with TLG < 760.5 compared to those with TLG ≥760.5 (p = 0.01 and = 0.005, respectively (Figure 5d,h).

On multivariate analysis, only larger tumour and presence of lymph node metastasis were significant prognostic factors for both OS and DFS (Table 3). Additionally, extensive Stage (≥IIB) was a significant prognosticator for DFS.

DISCUSSION

The present study investigated the prognostic significance of FDG-PET/CT metabolic parameters (SUV_{max}, SUV_{mean}, MTV and TLG) in locally advanced non-metastatic cervical cancer patients treated with definitive ChRT. We found that SUV_{max}, SUV_{mean}, MTV and TLG were significantly higher in patients with larger tumours (>4 cm) and partial regression or progressive disease. Although the FDG-PET/CT parameters were prognostic factors for OS and DFS in univariate analysis, they could not retain their significance in multivariate analysis. Similar to previous results, larger tumours and lymph node involvement were significant hazardous prognosticators for both OS and DFS, while extensive stage was a negative prognostic factor for DFS.

Clinical stage, tumour size and lymph node metastasis are the strongest prognostic factors in patients with locally advanced cervical cancer.[2,3,10] However, metabolic parameters derived from FDG-PET/CT has been investigated in some other series,

Table 2. Patient characteristics and correlations between positron emission tomography parameters and patient and tumour characteristics

Variables	*n*	%	SUV_{max} (Mean ± SD)	*p*	SUV_{mean} (Mean ± SD)	*p*	MTV (Mean ± SD)	*p*	TLG (Mean ± SD)	*p*
Age (median)	57 (22–83)									
Age (years)										
≤50	30	23	21.1 ± 9.6	0.7	12.5 ± 7.7	0.8	105.8 ± 82.4	0.7	1379.3 ± 1340±1	0.2
>50	99	77	18.4 ± 8.6		11.8 ± 6.2		101.1 ± 98.7		1494.6 ± 1127.4	
Pathology										
SCC	119	92	18.6 ± 8.6	0.1	11.7 ± 6.1	0.02	101.9 ± 96.7	0.9	1420.9 ± 952.4	0.3
Adenoca	10	8	24.2 ± 11.0		15.7 ± 9.9		105.8 ± 74.4		2025 ± 1178.7	
Tumour size (cm)										
≤4	30	23	14.2 ± 4.9	0.001	8.5 ± 3.0	0.002	49.4 ± 44.7	0.03	420.5 ± 319.9	<0.001
>4	99	77	20.4 ± 9.3		13.0 ± 7.0		118.2 ± 98.8		1785.1 ± 1131.4	
Stage										
<IIB	20	16	16.4 ± 8.3	0.7	10.6 ± 5.2	0.5	74.1 ± 69.2	0.4	1023.8 ± 945.7	0.3
≥IIB	109	84	19.5 ± 8.9		12.2 ± 6.7		107.4 ± 98.3		1549.2 ± 1056.7	
Ln metastasis										
Present	76	59	20.5 ± 8.7	0.7	13.1 ± 7.2	0.06	116.0 ± 86.5	0.8	1697.2 ± 1408.9	0.5
Absent	53	41	16.9 ± 8.7		10.3 ± 5.0		82.5 ± 73.5		11.38.8 ± 966.6	
Treatment response										
CR	66		16.6 ± 7.6	0.02	10.6 ± 5.9	0.02	70.9 ± 51.1	0.003	814.6 ± 711.3	<0.001
PR/PD	23		24.3 ± 9.8		15.3 ± 8.3		152.3 ± 101.7		2581.9 ± 2181.1	

Adenoca, adenocarcinoma; CR, complete response; ln, lymph node; MTV, metabolic tumour volume; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, standard deviation; SUV_{max}, maximum standardized uptake value; SUV_{mean}, average standardized uptake value; TLG, total lesion glycolysis.

for better assessing the tumour characteristics in patients treated with definitive modalities other than surgery. For this purpose, FDG-PET/CT is a valuable tool that incorporates metabolic tumour function with anatomical localization, and also an important imaging modality for both staging and assessing treatment response in cervical cancer patients. Several studies demonstrated that the higher SUV_{max} of primary tumour is associated with worse prognosis in cervical cancer patients.[5,6,11] However, SUV_{max} is a single-voxel measurement and it does not reflect the entire tumour metabolism.[31] Several FDG-PET/CT derived volumetric parameters were recently developed. The MTV is a novel potential prognostic factor representing the metabolic extent of the tumour and the size of viable tumour cells. The TLG represents both metabolic activity and tumour volume and is thought to be a more accurate parameter in survival.[23] These metrics are associated with high-risk prognostic factors, including extensive stage, larger tumours and lymph node metastasis.[23,31] In this current study, we also

Figure 4. Overall survival (a) and disease-free survival (b) curves for entire cohort.

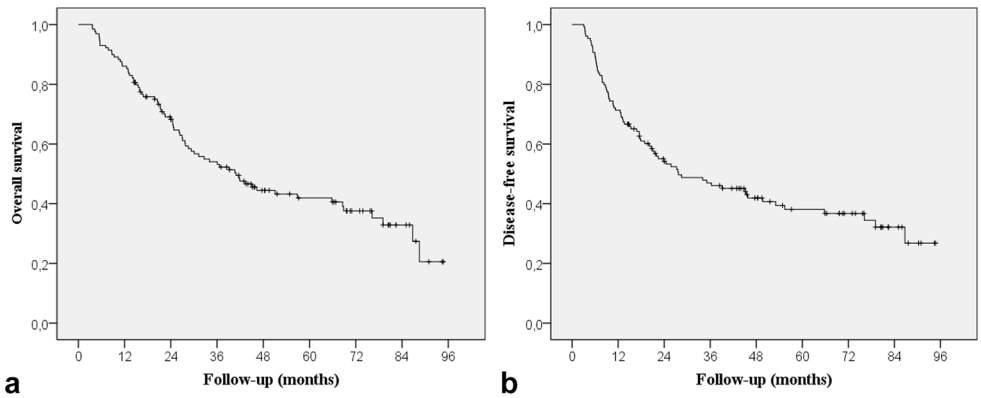
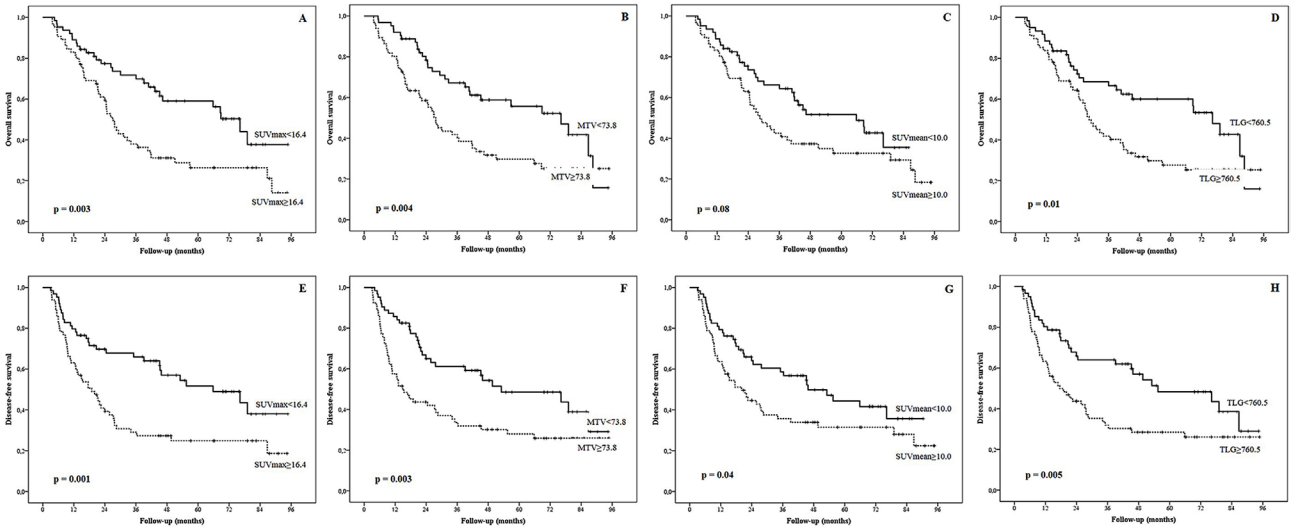


Figure 5. Kaplan–Meier patient survival estimates: overall survival for patients with SUV_{max} < 16.4 and ≥ 16.4 (a), MTV < 73.8 cm^3 and ≥ 73.8 cm^3 (b), SUV_{mean} < 10.0 and ≥ 10.0 (c), and TLG < 760.5 and ≥ 760.5 (d); disease-free survival for patients with SUV_{max} < 16.4 and ≥ 16.4 (e), MTV < 73.8 and ≥ 73.8 (f), SUV_{mean} < 10.0 and ≥ 10.0 (g), and TLG < 760.5 and ≥ 760.5 (h). MTV, metabolic tumour volume; SUV_{max}, maximum standardized uptake value; SUV_{mean}, average standardized uptake value; TLG, total lesion glycolysis.



demonstrated that FDG-PET/CT-derived volumetric parameters were all significantly associated with larger tumour size and also poor treatment response. The correlation between the tumour volume, tumour size and SUV has been studied in locally advanced cervical cancer.[11,25,32] Lee et al[32] found a significant difference in SUV_{max} according to the tumour size in 44 cervical cancer patients treated with surgery. The SUV_{max} was 16.3 ± 7.4 for tumours larger than 4 cm and 10.2 ± 6.8 for tumours 4 cm or smaller (p = 0.007). Similarly, Chung et al[25] showed that the pre-operative MTV was an independent prognostic factor for DFS in 63 cervical cancer patients treated with radical surgery. We have previously demonstrated that patients with a primary tumour SUV_{max} ≥15.6 had significantly larger tumours.[11] In this current study, although SUV_{max}, SUV_{mean}, MTV and TLG were significantly higher in patients with bulky tumours, only tumour size and lymph node metastasis were significant prognosticator for both OS and DFS.

Table 3. Multivariate analysis of prognostic factors for overall survival and disease-free survival

Variables	Risk factors	HR (95% CI)	*p*
Overall survival			
Stage	≥ IIB *vs* < IIB	2.49 (0.95–6.47)	0.06
Tumour size (cm)	> 4 *vs* ≤ 4	2.32 (1.15–4.69)	0.02
Lymph node metastasis	Present *vs* absent	1.99 (1.17–3.40)	0.01
SUV_{max}	≥ 16.4 *vs* < 16.4	1.96 (0.93–4.15)	0.08
MTV	≥ 73.8 *vs* < 73.8	1.69 (0.83–3.43)	0.15
SUV_{mean}	≥ 10.0 *vs* < 10.0	1.50 (0.73–3.12)	0.27
TLG	≥ 760.5 *vs* < 760.5	1.27 (0.58–2.78)	0.56
Disease-free survival			
Stage	≥ IIB *vs* < IIB	2.59 (1.01–6.67)	0.04
Tumour size (cm)	> 4 *vs* ≤ 4	2.51 (1.25–5.03)	0.01
Lymph node metastasis	Present *vs* absent	2.10 (1.25–5.03)	0.005
SUV_{max}	≥ 16.4 *vs* < 16.4	1.96 (0.96–4.00)	0.07
MTV	≥ 73.8 vs< 73.8	1.60 (0.80–3.21)	0.18
SUV_{mean}	≥ 10.0 *vs* < 10.0	1.44 (0.71–2.90)	0.32
TLG	≥ 760.5 *vs* < 760.5	1.19 (0.55–2.57)	0.65

HR, hazard ratio; MTV, metabolic tumour volume; SUV_{max}, maximum standardized uptake value; SUV_{mean}, average standardized uptake value; TLG, total lesion glycolysis.

The metabolic parameters of FDG-PET/CT were also analysed for their predictive values of OS and DFS in various trials (Table 4). Most of these studies were retrospective,[16,17,20,23,31,33] and some of them had prospective[18,19,21,22] designs. Chung et al[25] analysed the prognostic significance of MTV derived from FDG-PET/CT in 63 Stage IB to IIA cervical cancer patients treated with radical hysterectomy. The authors demonstrated that MTV ≥ 23.4 ml was an independent prognostic factor of DFS. In another surgical series conducted by Kim et al[24], patients with an MTV of >20 cm^3 had a significantly reduced DFS compared to patients with an MTV of ≤20 cm^3 in 45 Stage IA-IIB cervical cancer patients. Yoo et al[23] also demonstrated that TLG (cut-off 7600) and lymph node status were independent prognostic factors for event-free survival in 73 stage I–IV cervical cancer treated with surgery (44 patients) or definitive ChRT (28 patients). In a similar study with 49 patients (24 patients treated with surgery, 25 patients treated with ChRT), Micco et al[31] concluded that MTV and TLG were associated with high risk features, however, no multivariate analysis was performed in this study. The only study analysing 38 patients treated with concurrent ChRT, and the TLG ≥562 was an independent prognostic factor for OS.

Table 4. Published studies evaluating the importance of metabolic parameters derived from FDG-PET/CT in patients with cervical cancer

Author (year)	*n*	Study design	FIGO stage	Primary Treatment	Follow up (months)	Threshold	OS	DFS	Outcome
Leseur et al (2016)	53	Prosp.	IB-IVA	ChRT	50.0 (alive)	55% SUV_{max} 32% SUV_{max}	MTV1	MTV1, TLG2	5y OS: 77% 5y DFS: 69%
Ho et al (2016)	44	Prosp.	IB2-IVA	ChRT	56	ROC analysis	TLG	–	5y OS CMR: 82% 5y OS PD: 50%
Maharjan et al (2013)	26	Prosp.	Rec.	S, ChRT, ChT	NA	ROC analysis	SUV_{max}	SUV_{max}	NA
Crivellaro et al (2012)	69	Prosp.	IB1-IIA	S	29.2 (mean)	pN0 *vs* pN1	–	None (RFS)	NA
Hong et al (2016)	56	Retr.	IIB-IVA	ChRT	20	ROC analysis	–	TLG (RFS)	NA
Krhili et al (2016)	34	Retr.	IB2-IVA	ChRT	16	Pre-treatment *vs* per-treatment	SUV_{max}, MTV, TLG (Univariate)	SUV_{max}, MTV, TLG (Univariate)	NA
Chung et al (2016)	85	Retr.	IB-IIA	S	35	IFH at an SUV of 2.0 and ROC analysis	–	IFH (PFS)	Median PFS: 32 months
Micco et al (2014)	49	Retr.	IB-IVB	S, ChRT, ChT	17	42% SUV_{max}	MTV (Univariate)	MTV, TLG (Univariate)	NA
Akkas et al (2013)	58	Retr.	IIB-IVB	ChRT, ChT	22	CMR *vs* PD	None	None	NA
Yoo et al (2012)	73	Retr.	IB-IVB	S, ChRT, ChT	44.7 (mean)	Maximally selected log-rank statistics	None	TLG	NA
Current study (2017)	129	Retr.	IB-IVA	ChRT	50.5 (alive)	ROC analysis	None	None	5y OS: 42% 5y DFS: 38%

ChT, chemotherapy; ChRT, chemoradiotherapy; S, surgery; CMR, complete metabolic response; FDG-PET/CT, ^{18}F-fludeoxyglucose-positron emission tomography/CT; FIGO, International Federation of Gynecology and Obstetrics; PD, persistant disease; DFS, diseasefree survival; RFS, recurrence free survival; IFH, intratumoral ^{18}F-fludeoxyglucose uptake heterogeneity; NA, not available; OS, overall survival; Prosp, prospective; Retr, retrospective; ROC, receiver operating characteristics.

The studies had conflicting results because of several reasons. First, most of the series had fewer patients with limited follow up time; secondly, different cut-off value determination methods were used; thirdly, the treatment modalities were heterogeneous; and lastly, different SUV threshold values for defining MTV and TLG were preferred. In order to overcome these problems, we analysed only the patients treated with definitive ChRT; moreover, our study had a higher number of patients than previous studies and had a considerably acceptable follow up time. During MTV definition, we preferred a fixed threshold of SUV 2.5. The choice fixed SUV of 2.5 was largely based on studies demonstrating that SUV within range of 2.0 to 3.0 was optimal for defining malignant lesions, so this value minimized inclusion of unwanted physiological FDG uptake in normal tissues.[34,35] Also, the MTV measured by a threshold of 50% of SUV_{max} resulted in missing areas compared to MTV measured by a fixed threshold of SUV 2.5.[25,36] The optimal cut-off values for SUV_{max}, SUV_{mean}, MTV and TLG have not been yet established. In our study, we used ROC curve analysis to determine the thresholds as previous studies did.[17,19,20,22] However, our study demonstrated that volumetric FDG-PET/CT parameters were associated with larger tumours and poor post-treatment response, without significant survival benefit in multivariate analysis.

Although the cut-off values of metabolic and volumetric parameters derived from FDG-PET/CT varies in other studies, most of the authors reported that SUV_{max}, SUV_{mean} MTV and TLG were prognostic factors in univariate analysis,[17,18,20,22,23,31,33] which was our findings as well. However, there is a principal challenge while interpreting these results. In our study, we could not identify any of these metabolic parameters as statistically significant in multivariate analysis. Micco et al[31] and Krhili et al[33] did not perform multivariate analyses in their cohorts while concluding that MTV, TLG and/or SUV_{max} were prognostic factors in cervical cancer patients. Finally, in multivariate analysis, TLG has been reported as predictive for disease recurrence by Yoo et al[23] and Hong et al[20] and it was a significant predictive for OS in only one study conducted by Ho et al[19].

The present study has some limitations. The retrospective nature of the study is the largest limitation. Secondly, the inclusion of patients with various stages of disease may have introduced bias into the study, which may have affected the treatment outcomes. Last, we measured the tumour size in PET-CT images, measuring the tumour size in T_2 weighted MRI images should be more reliable. However, our findings, which were based on a larger and more homogenous patient population treated with definitive

ChRT only, and our follow up period, which was considerably longer than those of previous reports, would be more helpful for evaluating the significance of FDG-PET/CT metabolic parameters for survival and assessing the correlations of these parameters with other risk factors.

CONCLUSION

Conventional prognostic factors such as stage, tumour size and lymph node involvement are still the most reliable indicators related with patient outcome in patients with cervical cancer. In this study, we demonstrated that patients with higher SUV_{max}, SUV_{mean} and TLG, and larger MTV are associated with larger tumours and poor post-treatment response in patients treated with definitive ChRT. Although, metabolic parameters derived from FDG-PET/CT had a prognostic significance in univariate analysis, the significance was lost in multivariate analysis. However, the clinical benefit of using FDG-PET/CT metabolic parameters to evaluate the high risk patients among cervical cancer patients and to eventually change patient management still needs further clarification.

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