ASGO 2021 BANGKOK THAILAND

The 7th Biennial Meeting of Asian Society of Gynecologic Oncology

ASGO Asian Society of Gynecologic Oncology

November 25-27, 2021 THAILAND
Virtual Conference

"All accepted abstracts will be published in the JGO"

Abstract submission:
Open on June 1, 2021 - August 15, 2021
Abstract acceptance notification by:
September 15, 2021

Early Registration
Open : June 21, 2021
Close : September 30, 2021

Contact us: asgo2021@gmail.com

Online Registration: www.asgo2021.org

J Gynecol Oncol. 2021 Sep;32(5):e74
https://doi.org/10.3802/jgo.2021.32.e74
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Long-term outcomes of cervical cancer patients with complete metabolic response after definitive chemoradiotherapy

Cem Onal [1], **Ozan Cem Guler** [1], **Mehmet Reyhan** [2], **Ali Fuat Yapar** [2]

[1]Department of Radiation Oncology, Adana Dr. Turgut Noyan Research and Treatment Center, Baskent University Faculty of Medicine, Adana, Turkey
[2]Department of Nuclear Medicine, Baskent University Faculty of Medicine, Ankara, Turkey

Received: Dec 9, 2020
Revised: May 8, 2021
Accepted: May 23, 2021

Correspondence to
Cem Onal
Department of Radiation Oncology, Adana Dr. Turgut Noyan Research and Treatment Center, Baskent University Faculty of Medicine, Baraj Yolu 1 Durak, Seyhan, Adana 01120, Turkey.
E-mail: hcemonal@hotmail.com

ORCID iDs
Cem Onal
https://orcid.org/0000-0002-2742-9021
Ozan Cem Guler
https://orcid.org/0000-0001-6908-3412
Mehmet Reyhan
https://orcid.org/0000-0001-8163-1768
Ali Fuat Yapar
https://orcid.org/0000-0003-1715-4180

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: We investigated the importance of metabolic parameters measured with ^{18}F-fluorodeoxyglucose positron-emission tomography integrated with computed tomography (FDG-PET/CT) for predicting progression-free survival (PFS) and overall survival (OS) in cervical cancer with complete metabolic response (CMR) after chemoradiotherapy (ChRT).
Methods: The clinical data and PET parameters including standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of 122 patients having CMR in post-treatment ^{18}F-FDG-PET/CT delivered a median of 3.9 months after ChRT completion were analyzed.
Results: With a median follow-up of 8.4 years, 55 patients (45%) presented with disease a median of 19.7 months after ChRT. For SUVp, MTVp, TLGp, SUVln, MTVln, and TLGp, the cut-off values for OS determined by receiver operating curve analysis were 15.8, 48.7 cm^3, 552.3, 8.7, 7.0 cm^3, respectively. All metabolic PET parameters were significant prognostic factors for OS and PFS in univariate analysis. International Federation of Gynecology and Obstetrics (FIGO) stage was predictive of both OS and PFS, while pelvic and/or para-aortic lymph node metastasis were predictive of OS only. In multivariate analysis, FIGO stage ≥IIB, MTVp ≥49.8 cm^3, and TLGp ≥597.4 were predictive of worse OS. Advanced stage, presence of lymph node metastasis, higher TLGp, and larger MTVln were significant factors for poor PFS rates.
Conclusion: We found that advanced stage and higher TLGp values were significant predictors for poor survival and higher progression rates. Volumetric PET parameters could be used to predict treatment outcomes in patients with CMR after definitive ChRT.

Keywords: Cervical Cancer; Radiotherapy; Positron Emission Tomography; Prognostic Factor; Survival

INTRODUCTION

The treatment of choice for locally advanced cervical cancer is concurrent chemoradiotherapy (ChRT), and complete response is achieved in 70%–90% of patients [1,2]. ^{18}F-fluorodeoxyglucose positron-emission tomography integrated with computed tomography (FDG-PET/CT) incorporates metabolic tumor function with anatomic

Author Contributions
Data curation: O.C., G.O.C., R.M., Y.A.F.; Formal analysis: O.C., R.M.; Funding acquisition: G.O.C.; Investigation: O.C., R.M.; Methodology: O.C., R.M.; Project administration: G.O.C., Y.A.F.; Resources: Y.A.F.; Software: G.O.C., R.M.; Supervision: O.C., Y.A.F.; Visualization: Y.A.F.; Writing - original draft: O.C.; Writing - review & editing: O.C., Y.A.F.

localization. Previous studies demonstrate that patients with complete metabolic response (CMR) detected with post-treatment FDG-PET/CT have better outcomes than patients without CMR [3-7]. However, approximately 10%–20% of patients with CMR have disease recurrence [6-8]. We have recently demonstrated that CMR was observed in 82% of patients in post-treatment FDG-PET/CT and 21% of patients with CMR had disease recurrence [7]. Therefore, identifying prognostic factors for disease recurrence after CMR is important to improve treatment in this high-risk group.

Metabolic parameters measured with ^{18}F-FDG-PET/CT are indicators of tumor metabolism, as represented by semiquantitative measurements of standardized uptake value (SUV). Although SUVmax is an independent predictor of recurrence and survival in locally advanced cervical cancer patients [4,8,9], it is still unknown which metabolic biomarker is the most robust in accurately predicting individual prognosis in the post-treatment assessment of patients with cervical cancer. Some PET parameters, such as average SUV (SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), have been investigated in patients with cervical cancer [10-14]. The MTV is a novel potential prognostic factor that represents the metabolic extent of the tumor and the size of viable tumor cells. TLG represents both metabolic activity and tumor volume and is thought to be a more accurate parameter in survival compared to SUV [15].

The utility of metabolic PET parameters in cervical cancer patients with CMR after ChRT has not been well studied. Recently, Son et al. [6] evaluated a limited number of patients to assess the value of metabolic FDG-PET parameters in cervical cancer patients having CMR after definitive radiotherapy (RT), but the study had a relatively short follow-up period and included limited patient number. The aim of the present study was to assess the importance of metabolic parameters measured with ^{18}F-FDG-PET/CT for predicting recurrence and survival in patients with cervical cancer who have CMR after the completion of definitive ChRT with a relatively longer follow-up.

MATERIALS AND METHODS

1. Patients

The clinical data of 173 patients with biopsy-proven cervical cancer treated with definitive ChRT at our institution between November 2006 and August 2012 were retrospectively evaluated. After initial analysis, 16 patients were excluded due to absence of posttreatment PET/CT, 3 patients died before posttreatment PET/CT and 2 patients had undergone hysterectomy after CRT, and finally 152 patients with PET/CT before the start of ChRT and post-treatment PET/CT for response evaluation were evaluated. Patients with organ metastasis and those having malignant diseases other than cervical cancer were excluded.

All patients were treated with external beam RT and concurrent weekly 40 mg/m^2 cisplatin. High-dose rate brachytherapy (BRT) was applied at the end of external RT that was applied twice per week [7].

2. Treatment protocol

All patients received a combination of 3-dimensional conformal external beam RT (99 patients, 81%) or intensity-modulated RT (24 patients, 19%), as well as a weekly cisplatin (40 mg/m^2), followed by a high-dose rate BRT, as previously described [16]. The irradiation fields

https://doi.org/10.3802/jgo.2021.32.e74

encompassed the primary cervical tumor, whole uterus, and regional pelvic lymphatics. Boost dose was not applied to parametrial field or large tumors. An additional paraaortic field was added in patients with paraaortic lymph node metastasis.

3. PET/CT technique

The patients were imaged using a dedicated PET/CT system (Discovery-STE 8; General Electric Medical System, Milwaukee, WI, USA) as previously described [9]. Patients fasted for at least 6 hours before intravenous administration of 370 to 555 MBq (10–15 mCi) FDG. Pre-injection blood glucose levels were measured to ensure they were below 150 mg/dL. During the distribution phase, the patients laid supine in a quiet room. Combined image acquisition began 60 minutes after FDG injection. The patients were scanned on a flat-panel carbon fiber 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 the 3-dimensional mode from the base of the skull to the inferior border of the pelvis (6–7 bed positions, 3 minutes per bed position) without repositioning the patient on the table. Computed tomographic 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 physiologic uptake from pathologic uptake.

4. Image analysis

The volumetric region of interest (ROI) around the outline of the primary tumor was placed on the axial PET/CT images using the semi-automatic software. Each observer, for every tumor lesion, manually delineated a mask, which is a ROI including the tumor, excluding non-tumor structures (e.g. nearby blood vessels) on the PET/CT scan. For each FDG-PET/CT study, the SUVmax, SUVmean, MTV, and TLG values of the primary tumor and metastatic lymph nodes were automatically generated from the ROI. The ROI borders were manually adjusted by visual inspection of the primary tumor to avoid overlap on adjacent FDG-avid structures. The MTV was defined as the regions equal to or greater than SUV of 2.5, and the TLG was calculated by multiplying SUVmean and MTV [10,12,13]. In each patient, the SUVmax was designated as the highest value of SUV of the primary tumor (SUVp) and lymph nodes (SUVln). The MTV and TLG were also obtained for the primary tumor (MTVp and TLGp) and metastatic lymph nodes (MTVln and TLGln), which were defined as the sums of the MTV and TLG values of each metastatic lymph node.

5. Clinical follow-up

In conjunction with a gynecologic oncologist, they monitored the patients every 3 months for the first 2 years, every 6 months until year 5, and annually thereafter. Complete physical and gynecologic examinations were periodically performed, as well as routine complete blood cell counts, serum biochemical testing, and chest X-rays. However, biopsies were reserved for suspicious lesions. To gauge treatment response, PET-CT scans were conducted at least 3 months after completing primary treatment. In patients with CMR, FDG-PET/CT is not routinely done until there is a suspicious lesion detected with other radiological imaging modalities or during gynecological examination. For metabolic response evaluation 'Positron Emission tomography Response Criteria In Solid Tumors' v1.0 was used [17]. Highest SUV_{max} was recorded for both PET/CT studies irrespective of number of lesions. The CMR was defined as FDG-PET uncovering no evidence of local or distant disease. Partial metabolic response (PMR) was defined as the persistence of FDG uptake exceeding the background

https://doi.org/10.3802/jgo.2021.32.e74

level in the liver at the site of initial disease, whereas progressive disease (PD) was defined as a new site of FDG uptake on the PET scan [3].

6. Statistical analysis

All statistical analyses were performed using standard software (SPSS version 20;IBM Corp., Chicago, IL, USA). The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS). The time to event was calculated as the time from the date of diagnosis to the date of the first finding in a clinical or imaging examination that suggested disease recurrence. The χ^2 or Student's t-tests were used to analyze the differences in clinical and pathological factors between patients with CMR and those without CMR. Both OS and PFS rates were estimated by the Kaplan-Meier method. Receiver operating characteristic (ROC) curves were generated to determine the cut-off values of PET parameters for predicting recurrence and survival that yielded the optimal sensitivity and specificity. Univariate analysis was performed using the log-rank test, and multivariate analysis was performed with the Cox proportional hazards model, using covariates with a p-value less than 0.10 in univariate analysis. All p-values <0.05 were considered statistically significant.

RESULTS

1. Patient characteristics

Post-treatment PET-CT images were taken within a median of 3.9 months (range, 3.0–9.8 months) after the completion of ChRT. One hundred twenty-two patients (80%) had CMRs on follow-up FDG-PET, whereas 23 (13%) and 7 patients (5%) had PMR and PD, respectively.

The characteristics of patients with CMR and those without CMR after ChRT are included in **Table 1**. There were no significant differences in patient and tumor characteristics between the 2 groups. In 122 patients with CMR, most patients had International Federation of Gynecology and Obstetrics (FIGO) stage IIB disease, tumor diameter ≥4 cm, and squamous cell carcinoma histology. The median OS was 9.0 years (95% confidence interval [CI]=5.8–

Table 1. Patient and tumor characteristics in patients with CMR and non-CMR

Characteristics	CMR (n=122)	Non-CMR (n=30)	p-value
Median age (yr)	58 (30–84)	57 (21–86)	0.41
FIGO stage			0.32
IB2	13 (11)	3 (10)	
IIA	6 (5)	0 (0)	
IIB	72 (59)	15 (50)	
IIIA	12 (10)	2 (7)	
IIIB	19 (16)	8 (26)	
IVA	0 (0)	2 (7)	
Tumor size			0.37
<4 cm	18 (15)	3 (10)	
≥4 cm	104 (85)	27 (90)	
Histology			0.46
Squamous cell carcinoma	115 (94)	27 (90)	
Adenocarcinoma	7 (6)	3 (10)	
Lymph node metastasis			0.21
None	60 (49)	11 (37)	
Pelvic lymph node	51 (42)	15 (50)	
Para-aortic lymph node	11 (9)	4 (13)	

Values are presented as number of patients (%).
CMR, complete metabolic response; FIGO, International Federation of Gynecology and Obstetrics.

https://doi.org/10.3802/jgo.2021.32.e74

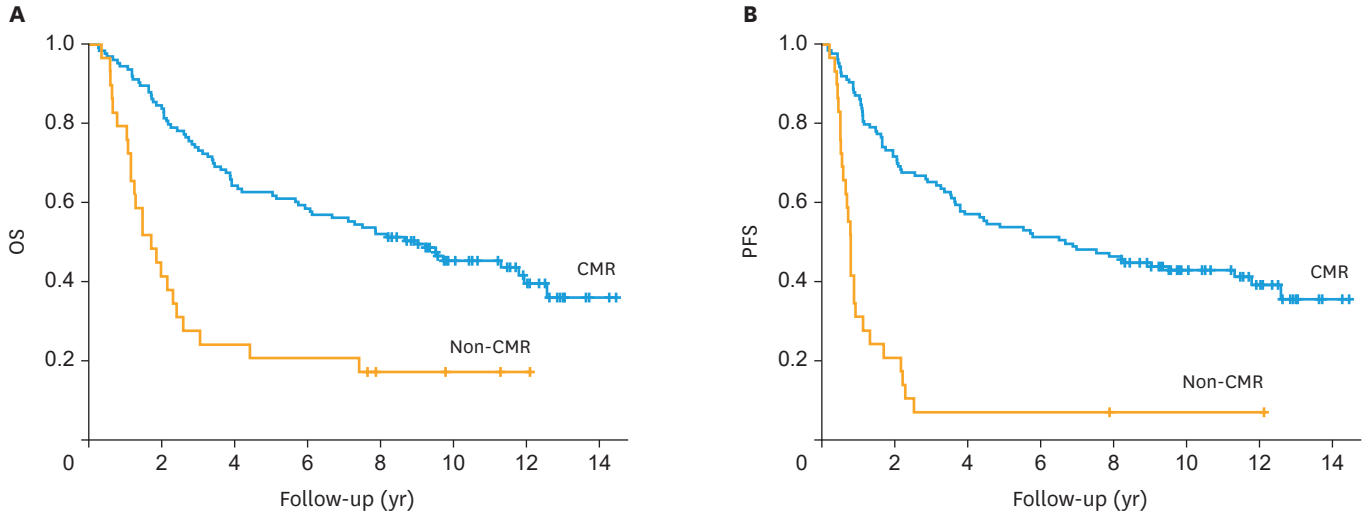

Fig. 1. (A) OS and (B) PFS graphs of patients with CMR (blue line) and non-CMR (yellow line).
CMR, complete metabolic response; OS, overall survival; PFS, progression-free survival.

12.2 years) for patients with CMR and 1.7 years (95% CI=1.0–2.5 years; p<0.001) for patients with non-CMR (**Fig. 1A**). Similarly, median PFS was significantly higher in patients with CMR detected in post-treatment ^{18}F-FDG-PET/CT compared to those without CMR (6.7 years [95% CI=3.4–9.9 years] vs. 0.8 years [95% CI=0.7–2.5 years]; p<0.001) (**Fig. 1B**).

All patients were treated with concurrent ChRT: 108 patients (89%) completed at least 4 cycles of ChRT, 10 patients (8%) completed 3 cycles, and 4 patients (3%) received 2 cycles of ChRT during RT. The median total and fraction external RT dose was 50.4 Gy (range, 45.0–56 Gy) and 1.8 Gy (range, 1.8–2.0 Gy), respectively. The median BRT dose was 28 Gy (range, 21–28 Gy) delivered in a median of 4 fractions (range, 3–5 fractions).

2. Treatment outcome of patients with CMR

The median follow-up time for the entire cohort was 8.4 years (range, 0.3–14.5 years) and for survivors was 10.5 years (range, 8.2–14.5 years). Of the 122 patients with post-treatment CMR, 55 (45%) developed local, locoregional, or distant failure a median of 19.7 months (range, 1.9–99.4 months) after completion of ChRT. Of the 55 patients with disease recurrence, 17 patients (31%) had a local or locoregional failure, 31 patients (56%) developed distant metastasis, and 7 patients (13%) had both locoregional and distant failures. At the time of the last follow-up, 53 patients (44%) were alive (3 patients (3%) with disease) and 69 patients (56%) had died; 52 patients (42%) died due to disease progression and 17 patients (14%) died from other causes.

Of 30 patients with non-CMR after definitive CRT, 6 (20%) had local or locoregional recurrence, 17 (57%) had distant failure and 7 (23%) had both locoregional failure and distant metastasis. During last follow-up time, only 2 patients (7%) were alive. These 2 patients had isolated local recurrence, and were treated with surgery. Twenty-eight patients (93%) with non-CMR had died because of disease.

3. PET parameters

The median SUVp, MTVp, and TLGp values were 14.5 (range, 4.1–42.3), 36.3 cm^3 (range, 4.1–127.8 cm^3), and 456.6 (range, 16.8–2523.6), respectively. For metastatic lymph nodes,

https://doi.org/10.3802/jgo.2021.32.e74

the median values of SUVln, MTVln, and TLGln were 6.5 (range, 2.7–22.5), 11.6 cm^3 (range, 1.8–56.9 cm^3), and 76.5 (range, 3.6–1,280.5), respectively.

For SUVp, MTVp, TLGp, SUVln, MTVln, and TLGln, the cut-off values calculated by ROC curve analysis for determining OS were 15.8, 48.7 cm^3, 552.3, 8.7, 7.0 cm^3, and 24.6, respectively. For disease recurrence, the cut-off values were 19.9, 49.8 cm^3, 597.4, 9.1, 7.3 cm^3, and 25.2 for SUVp, MTVp, TLGp, SUVln, respectively.

4. Prognostic factors

The metabolic parameters of primary tumor and metastatic lymph nodes were significant predictors for OS and PFS in univariable analysis (**Figs. 2** and **3**). Pelvic and/or para-aortic lymph node metastasis was predictive of both OS and PFS in univariate analysis, while FIGO stage was predictive of OS only (**Tables 2** and **3**). A borderline significance was observed in lymph node metastasis for PFS. All metabolic PET parameters were significant prognostic factors for OS and PFS in univariate analysis. In multivariate analysis, FIGO stage ≥IIB, MTVp ≥49.8 cm^3, and TLGp ≥597.4 were predictive of worse OS (**Table 2**). Advanced stage, presence of lymph node metastasis, higher TLGp, and larger MTVln were significant factors for poor PFS rates (**Table 3**).

In subgroup analysis, all metabolic PET parameters were significant prognostic factors for local recurrence and distant metastasis, and additional significant predictor for distant metastasis was presence of regional lymph node metastasis (p=0.03). However,

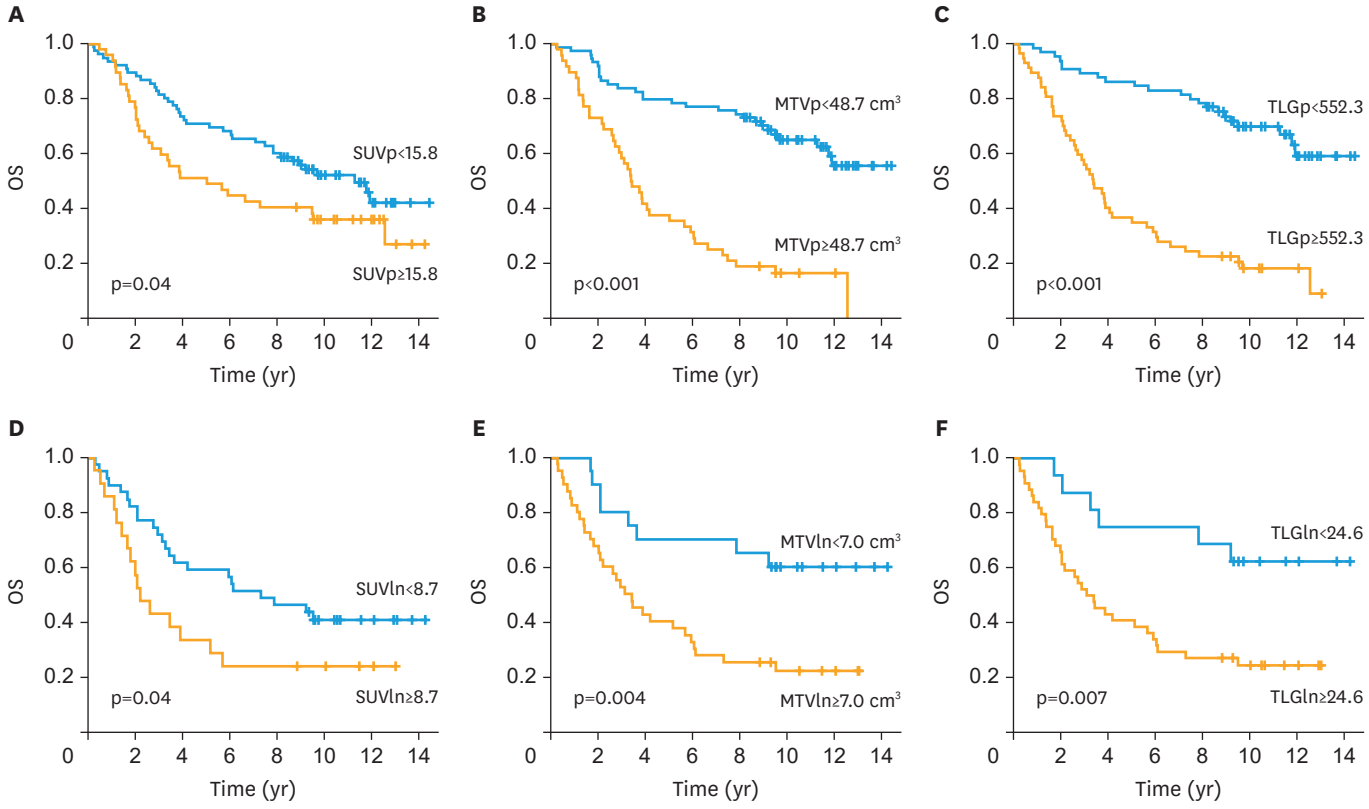

Fig. 2. Kaplan-Meier patient survival estimates: OS for patients with SUVp <15.8 and ≥15.8 (A), MTVp < 48.7 cm^3 and ≥48.7 cm^3 (B), TLGp < 552.3 and ≥ 552.3 (C), SUVln < 8.7 and ≥ 8.7 (D), MTVln <7.0 cm^3 and ≥7.0 cm^3 (E), TLGln < 24.6 and ≥ 24.6 (F).
MTV, metabolic tumor volume; OS, overall survival; SUV, standardized uptake value; TLG, total lesion glycolysis.

https://doi.org/10.3802/jgo.2021.32.e74

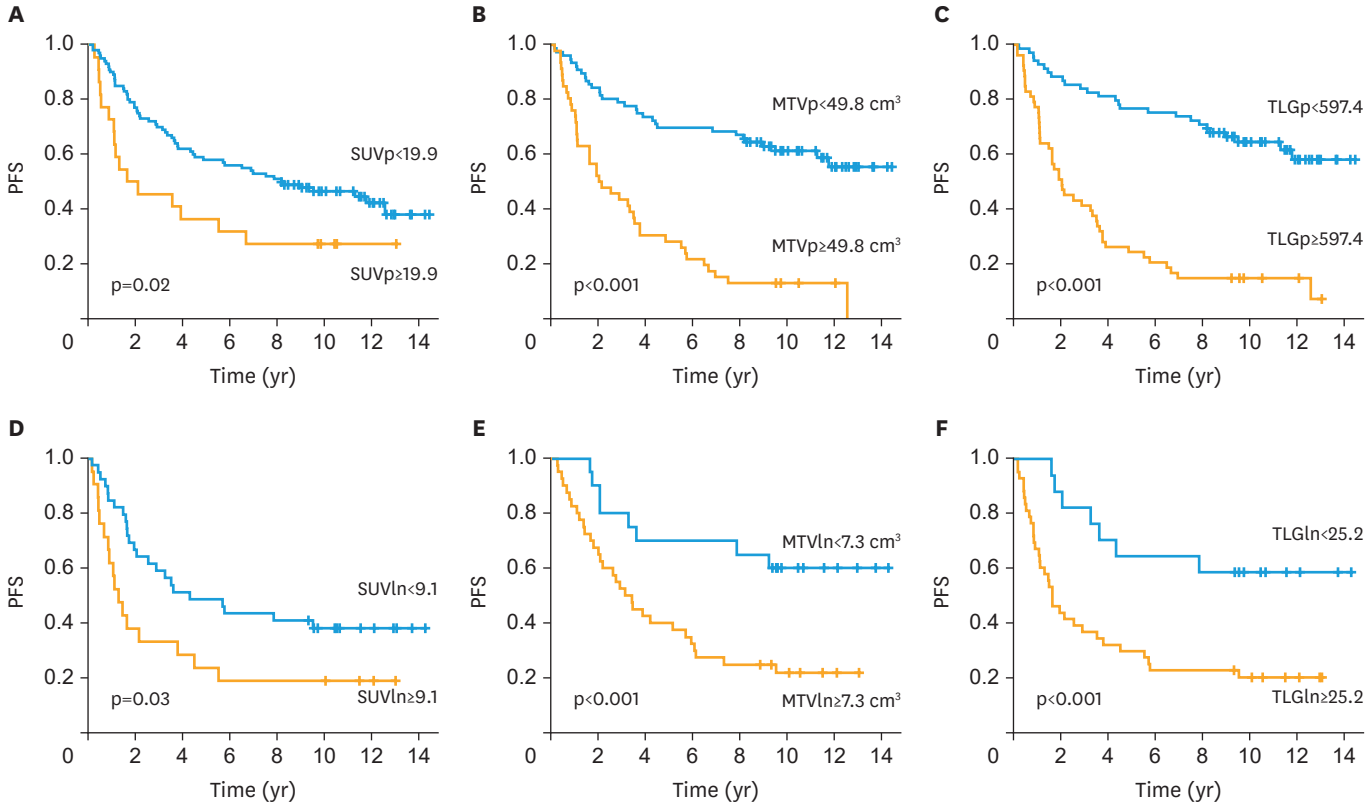

Fig. 3. Kaplan-Meier patient survival estimates: PFS for patients with SUVp <19.9 and ≥19.9 (A), MTVp <49.8 cm³ and ≥49.8 cm³ (B), TLGp <597.4 and ≥597.4 (C), SUVln <9.1 and ≥9.1 (D), MTVln <7.3 cm³ and ≥7.3 cm³ (E), TLGln <25.2 and ≥25.2 (F).
MTV, metabolic tumor volume; OS, overall survival; SUV, standardized uptake value; TLG, total lesion glycolysis.

Table 2. Univariate and multivariate analyses for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≤50 yr vs. >50 yr)	1.67 (0.88–3.19)	0.12		
Histology (SCC vs. adenocarcinoma)	1.14 (0.46–2.83)	0.78		
FIGO stage (<IIB vs. ≥IIB)	2.41 (1.10–5.27)	0.03	2.53 (1.02–7.34)	0.04
Tumor size (<4 cm vs. ≥4 cm)	1.49 (0.71–3.11)	0.29		
Lymph node stage (N0 vs. N1/N2)	1.89 (1.17–3.04)	0.009		
Primary tumor SUVmax (<19.9 vs. ≥19.9)	1.61 (1.01–2.59)	0.04		
Primary tumor MTV (<49.8 cm³ vs. ≥49.8 cm³)	4.16 (2.54–6.82)	<0.001	4.13 (2.51–6.78)	<0.001
Primary tumor TLG (<597.4 vs. ≥597.4)	4.61 (2.75–7.73)	<0.001	2.21 (1.06–4.61)	0.03
Nodal SUVmax (<9.1 vs. ≥9.1)	1.90 (1.04–3.62)	0.04		
Nodal MTV (<7.3 cm³ vs. ≥7.3 cm³)	2.98 (1.36–6.52)	0.004		
Nodal TLG (<24.6 vs. ≥24.6)	3.16 (1.32–7.57)	0.007		

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; MTV, metabolic tumor volume; SCC, squamous cell carcinoma; SUV, standardized uptake value; TLG, total lesion glycolysis.

no significant factor for predicting local recurrence and distant metastasis was found in multivariate analysis.

DISCUSSION

The present study investigated the predictive role of clinical and metabolic parameters for treatment outcomes in patients with cervical cancer who were treated with definitive ChRT

https://doi.org/10.3802/jgo.2021.32.e74

Table 3. Univariate and multivariate analyses for progression free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≤50 yr vs. >50 yr)	1.54 (0.83–2.87)	0.17		
Histology (SCC vs. adenocarcinoma)	1.18 (0.48–2.93)	0.72		
FIGO stage (<IIB vs. ≥IIB)	2.03 (0.97–4.24)	0.06	4.11 (0.98–7.22)	0.05
Tumor size (<4 cm vs. ≥4 cm)	1.59 (0.76–3.31)	0.22		
Lymph node stage (N0 vs. N1/N2)	1.95 (1.22–3.12)	0.005	1.48 (1.09–2.39)	0.04
Primary tumor SUVmax (<19.9 vs. ≥19.9)	1.92 (1.10–3.36)	0.02		
Primary tumor MTV (<49.8 cm^3 vs. ≥49.8 cm^3)	4.11 (2.54–6.65)	<0.001		
Primary tumor TLG (<597.4 vs. ≥597.4)	4.64 (2.83–7.60)	<0.001	2.31 (1.14–4.68)	0.02
Nodal SUVmax (<9.1 vs. ≥9.1)	2.03 (1.09–3.79)	0.03		
Nodal MTV (<7.3 cm^3 vs. ≥7.3 cm^3)	2.86 (1.40–5.86)	0.004	2.24 (1.05–4.74)	0.04
Nodal TLG (<25.2 vs. ≥25.2)	3.26 (1.44–7.39)	0.005		

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; MTV, metabolic tumor volume; SCC, squamous cell carcinoma; SUV, standardized uptake value; TLG, total lesion glycolysis.

and who exhibited a CMR observed a median of 3.9 months after completion of treatment. Although patients with CMR had better survival rates than those without CMR, 45% of patients with CMR had disease progression 19.7 months after completion of ChRT. After a median follow-up of 8.4 years, advanced stage and higher TLG values of the primary tumor were identified as important prognostic factors predicting OS and PFS. Additional prognostic factors for worse OS were larger MTVp and lymph node metastasis and for disease progression, MTVln. We also found that most disease recurrences presented as distant metastasis, which suggests a need for effective systemic treatment.

The most relevant predictive factors for disease recurrence, either local or distant, are FIGO stage, lymph node status, and treatment response evaluated clinically or with radiological images [18,19]. However, in some instances, clinical examination or conventional imaging modalities may under assess disease recurrence [20]. Consequently, various functional imaging techniques have been investigated for the purpose of assessing and monitoring tumor response before treatment. To better evaluate the disease recurrence, metabolic response demonstrated by post-treatment ^{18}F-FDG-PET/CT has been used for predicting patient outcomes [2,3,6,7,12,14,21]. The metabolic CMR rate on ^{18}F-FDG-PET/CT after definitive ChRT in cervical cancer patients is 70%–80%, and patients with CMR at post-treatment PET-CT have better outcomes than those without CMR [3,4,7]. However, most of these studies assessed the treatment response by visual interpretation of the primary tumor via SUVmax values. The SUVmax is a single-voxel measurement; therefore, it is inadequate to reflect the entire tumor metabolism properly [15]. Some studies used other FDG-PET/CT volumetric parameters including MTV and TLG for predicting the treatment response [6,14]. Lima et al. [14] demonstrated that pretreatment MTV and TLG were significant predictors for treatment response in 82 cervical cancer patients treated with ChRT. Son et al. [6] found that SUVmax or MTVln are prognostic factors for disease recurrence and survival in 61 locally advanced cervical cancer patients having CMR after definitive ChRT. However, the authors failed to demonstrate the benefit of MTV and TLG of the primary tumor in patients with CMR, which may be due to their limited patient number. Few studies evaluated the prognostic importance with potential threshold value of volume-based parameters of FDG-PET/CT and apparent diffusion coefficient (ADC) for predicting treatment outcomes in patients with cervical cancer [22]. Ueno et al. [22] demonstrated that pre-treatment volume-based quantitative parameters of 18F-FDG PET had better potential than ADC histogram for predicting treatment response and survival in 21 patients with locally advanced cervical cancer. In this current study, rather than SUVmax of the primary tumor, we demonstrated

https://doi.org/10.3802/jgo.2021.32.e74

that TLGp was a predictive factor for both OS and PFS and MTVp was a prognosticator for OS in patients having CMR after definitive ChRT.

Lymph node metastasis is a significant predictor for survival and disease recurrence for patients with locally advanced cervical cancer [19,23] and for patients with CMR after definitive ChRT [6,7]. Furthermore, metabolic parameters of metastatic lymph nodes measured from FDG-PET/CT are predictive of treatment outcomes in cervical cancer patients receiving ChRT [6,24-26]. However, only Son et al. [6] demonstrated nodal SUVmax is a prognostic factor for disease recurrence and nodal MTV is a predictive factor for OS in patients with CMR after definitive ChRT. In our present study, we evaluated metabolic parameters for primary tumors and metastatic lymph nodes separately, and we found that MTVln was a predictive factor for PFS. Because the sensitivity and specificity of FDG-PET/CT for detection of pelvic lymph nodes metastasis were nearly 80% and 100%, respectively [27], MTV of metastatic lymph nodes measured with PET/CT may be a good surrogate for assessing disease progression in cervical cancer patients having CMR after ChRT.

Our study has some limitations. The retrospective nature of our study is the largest limitation. Second, the partial volume effects of PET/CT in detecting small lymph nodes may underestimate the number of metastatic lymph nodes. The reported false-positive rates of FDG-PET/CT for lymph nodes in cervical cancer is between 5% and 30%, which is mainly caused by infections and other inflammatory conditions [28-31]. Because all patients were treated with definitive ChRT, histopathologic confirmation of FDG-positive lymph nodes was not performed. Last the post-therapy metabolic response evaluations with FDG-PET/CT were performed at different times varying from 3 to 10 months (median, 4 months). The guidelines recommend follow-up evaluation every 3–6 months for the first 2 years, because more than three-fourths of recurrences will occur within the first 2–3 years after the initial treatment [32,33]. Since RT effects last longer, evaluating treatment response in the long term (>3 months) is critical for distinguishing between resistant and recurrent disease. Additionally, physical examination for cervical cancer accounted for the highest detection rate when compared with cytologic evaluation and imaging modalities [34]. Although the post-treatment PET-CT was delivered in varied time period, only 9 patients (7%) had post-treatment PET-CT taken > 6 months after completion of treatment and all of these patients were evaluated with either CT or MRI. However, for evaluation of treatment response, all patients had undergone a detailed gynecological examination every 3 months for the first 2 years. Therefore, although we could not make a conclusion regarding the optimal timing of posttherapy PET-CT, at least a detailed gynecological examination was performed at each visit.

Despite these limitations, our study is important in demonstrating the clinical outcomes in patients with CMR who had a relatively longer median follow-up time (8.7 years) than in previous reports and in a group with more high-risk features [6,7]. In our previous report, which had a median follow-up of 28.7 months, we could not demonstrate the prognostic impact of metabolic PET parameters in cervical cancer patients with CMR after definitive ChRT because we only assessed SUVmax of the primary tumor [7]. However, in the current study with the same patient population and a longer follow-up, we analyzed additional metabolic parameters including MTV and TLG for both the primary tumor and metastatic lymph nodes. In contrast to our previous report, we found that MTV and TLG of the primary tumor be used to predict OS and primary tumor TLG and nodal MTV were independent prognosticators for PFS. Additionally, disease progression increased from 21% to 45% a median of 19.7 months after completion of ChRT. This increase in disease progression,

mostly as distant metastasis, after longer follow-up addresses the importance of a specific biomarker for intensifying the treatment strategies. Our study differs from a previous study that demonstrates the feasibility of metabolic parameters in cervical cancer with CMR after ChRT in having a higher patient number (61 patients vs. 122 patients) and relatively longer follow-up (56.6 months vs. 8.7 years) [6].

Our findings, based on a larger patient population and longer follow-up, clearly demonstrate that extensive stage (>IIB) and higher TLGp are significant predictors for poor survival and higher progression rates. In addition to SUVmax, MTV and TLG for primary tumors and metastatic lymph nodes could be useful to predict high-risk patients even with having CMR after definitive ChRT. Identification of these high-risk factors is important for need of systemic ChRT or other targeted treatment modalities.

REFERENCES

1. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-53.
PUBMED | CROSSREF
2. Park TK, Kwon JY, Kim SW, Kim SH, Kim SN, Kim GE. Patterns of treatment failure following radiotherapy with combination chemotherapy for patients with high-risk stage IIB cervical carcinoma. Int J Clin Oncol 2004;9:120-4.
PUBMED | CROSSREF
3. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Metabolic response on post-therapy FDG-PET predicts patterns of failure after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2012;83:185-90.
PUBMED | CROSSREF
4. Beriwal S, Kannan N, Sukumvanich P, Richard SD, Kelley JL, Edwards RP, et al. Complete metabolic response after definitive radiation therapy for cervical cancer: patterns and factors predicting for recurrence. Gynecol Oncol 2012;127:303-6.
PUBMED | CROSSREF
5. Schwarz JK, Lewis JS Jr, Pfeifer J, Huettner P, Grigsby P. Prognostic significance of p16 expression in advanced cervical cancer treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys 2012;84:153-7.
PUBMED | CROSSREF
6. Son SH, Jeong SY, Chong GO, Lee YH, Park SH, Lee CH, et al. Prognostic value of pretreatment metabolic PET parameters in cervical cancer patients with metabolic complete response after concurrent chemoradiotherapy. Clin Nucl Med 2018;43:e296-303.
PUBMED | CROSSREF
7. Onal C, Reyhan M, Guler OC, Yapar AF. Treatment outcomes of patients with cervical cancer with complete metabolic responses after definitive chemoradiotherapy. Eur J Nucl Med Mol Imaging 2014;41:1336-42.
PUBMED | CROSSREF
8. Siva S, Herschtal A, Thomas JM, Bernshaw DM, Gill S, Hicks RJ, et al. Impact of post-therapy positron emission tomography on prognostic stratification and surveillance after chemoradiotherapy for cervical cancer. Cancer 2011;117:3981-8.
PUBMED | CROSSREF
9. Onal C, Reyhan M, Parlak C, Guler OC, Oymak E. Prognostic value of pretreatment 18F-fluorodeoxyglucose uptake in patients with cervical cancer treated with definitive chemoradiotherapy. Int J Gynecol Cancer 2013;23:1104-10.
PUBMED | CROSSREF
10. Guler OC, Torun N, Yildirim BA, Onal C. Pretreatment metabolic tumour volume and total lesion glycolysis are not independent prognosticators for locally advanced cervical cancer patients treated with chemoradiotherapy. Br J Radiol 2018;91:20170552.
PUBMED | CROSSREF
11. Yoo J, Choi JY, Lee KT, Heo JS, Park SB, Moon SH, et al. Prognostic significance of volume-based metabolic parameters by (18)F-FDG PET/CT in gallbladder carcinoma. Nucl Med Mol Imaging 2012;46:201-6.
PUBMED | CROSSREF

12. Chung HH, Kim JW, Han KH, Eo JS, Kang KW, Park NH, et al. Prognostic value of metabolic tumor volume measured by FDG-PET/CT in patients with cervical cancer. Gynecol Oncol 2011;120:270-4.
PUBMED | CROSSREF
13. Herrera FG, Breuneval T, Prior JO, Bourhis J, Ozsahin M. [(18)F]FDG-PET/CT metabolic parameters as useful prognostic factors in cervical cancer patients treated with chemo-radiotherapy. Radiat Oncol 2016;11:43.
PUBMED | CROSSREF
14. Lima GM, Matti A, Vara G, Dondi G, Naselli N, De Crescenzo EM, et al. Prognostic value of posttreatment ^{18}F-FDG PET/CT and predictors of metabolic response to therapy in patients with locally advanced cervical cancer treated with concomitant chemoradiation therapy: an analysis of intensity- and volume-based PET parameters. Eur J Nucl Med Mol Imaging 2018;45:2139-46.
PUBMED | CROSSREF
15. Miccò M, Vargas HA, Burger IA, Kollmeier MA, Goldman DA, Park KJ, et al. Combined pre-treatment MRI and 18F-FDG PET/CT parameters as prognostic biomarkers in patients with cervical cancer. Eur J Radiol 2014;83:1169-76.
PUBMED | CROSSREF
16. Onal C, Arslan G, Topkan E, Pehlivan B, Yavuz M, Oymak E, et al. Comparison of conventional and CT-based planning for intracavitary brachytherapy for cervical cancer: target volume coverage and organs at risk doses. J Exp Clin Cancer Res 2009;28:95.
PUBMED | CROSSREF
17. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50 Suppl 1:122S-150S.
PUBMED | CROSSREF
18. Jacobs AJ, Faris C, Perez CA, Kao MS, Galakatos A, Camel HM. Short-term persistence of carcinoma of the uterine cervix after radiation. An indicator of long-term prognosis. Cancer 1986;57:944-50.
PUBMED | CROSSREF
19. Atahan IL, Onal C, Ozyar E, Yiliz F, Selek U, Kose F. Long-term outcome and prognostic factors in patients with cervical carcinoma: a retrospective study. Int J Gynecol Cancer 2007;17:833-42.
PUBMED | CROSSREF
20. Narayan K, Fisher RJ, Bernshaw D, Shakher R, Hicks RJ. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. Int J Gynecol Cancer 2009;19:912-8.
PUBMED | CROSSREF
21. Grigsby PW, Siegel BA, Dehdashti F, Mutch DG. Posttherapy surveillance monitoring of cervical cancer by FDG-PET. Int J Radiat Oncol Biol Phys 2003;55:907-13.
PUBMED | CROSSREF
22. Ueno Y, Lisbona R, Tamada T, Alaref A, Sugimura K, Reinhold C. Comparison of FDG PET metabolic tumour volume versus ADC histogram: prognostic value of tumour treatment response and survival in patients with locally advanced uterine cervical cancer. Br J Radiol 2017;90:20170035.
PUBMED | CROSSREF
23. Manetta A, Delgado G, Petrilli E, Hummel S, Barnes W. The significance of paraaortic node status in carcinoma of the cervix and endometrium. Gynecol Oncol 1986;23:284-90.
PUBMED | CROSSREF
24. Sarker A, Im HJ, Cheon GJ, Chung HH, Kang KW, Chung JK, et al. Prognostic implications of the SUVmax of primary tumors and metastatic lymph node measured by 18F-FDG PET in patients with uterine cervical cancer: a meta-analysis. Clin Nucl Med 2016;41:34-40.
PUBMED | CROSSREF
25. Chung HH, Cheon GJ, Kang KW, Kim JW, Park NH, Song YS. Preoperative PET/CT FDG standardized uptake value of pelvic lymph nodes as a significant prognostic factor in patients with uterine cervical cancer. Eur J Nucl Med Mol Imaging 2014;41:674-81.
PUBMED | CROSSREF
26. Onal C, Guler OC, Reyhan M, Yapar AF. Prognostic value of 18F-fluorodeoxyglucose uptake in pelvic lymph nodes in patients with cervical cancer treated with definitive chemoradiotherapy. Gynecol Oncol 2015;137:40-6.
PUBMED | CROSSREF
27. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, Ihling C, Högerle S, Mix M, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. Radiology 2001;218:776-82.
PUBMED | CROSSREF
28. Ramirez PT, Jhingran A, Macapinlac HA, Euscher ED, Munsell MF, Coleman RL, et al. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective

correlation of surgical findings with positron emission tomography/computed tomography findings. Cancer 2011;117:1928-34.
PUBMED | CROSSREF

29. Leblanc E, Gauthier H, Querleu D, Ferron G, Zerdoud S, Morice P, et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. Ann Surg Oncol 2011;18:2302-9.
PUBMED | CROSSREF

30. Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med 2000;27:822-32.
PUBMED | CROSSREF

31. Onal C, Oymak E, Findikcioglu A, Reyhan M. Isolated mediastinal lymph node false positivity of [18F]-fluorodeoxyglucose-positron emission tomography/computed tomography in patients with cervical cancer. Int J Gynecol Cancer 2013;23:337-42.
PUBMED | CROSSREF

32. Elit L, Fyles AW, Oliver TK, Devries-Aboud MC, Fung-Kee-Fung Mmembers of the Gynecology Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. Follow-up for women after treatment for cervical cancer. Curr Oncol 2010;17:65-9.
PUBMED | CROSSREF

33. Greer BE, Koh WJ, Abu-Rustum NR, Apte SM, Campos SM, Chan J, et al. Cervical cancer. J Natl Compr Canc Netw 2010;8:1388-416.
PUBMED | CROSSREF

34. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. Gynecol Oncol 2007;107:S241-7.
PUBMED | CROSSREF