





The Prognostic Value of Sequential ^{18}F -FDG PET/CT Metabolic Parameters in Outcomes of Upper-Third Esophageal Squamous Cell Carcinoma Patients Treated with Definitive Chemoradiotherapy

Le Ngoc Ha^{1,*}  Nguyen Dinh Chau^{2,*} Bui Quang Bieu² Mai Hong Son¹ 

¹Department of Nuclear Medicine, Hospital 108, Hanoi, Vietnam

²Department of Radiation Oncology and Radiosurgery, Hospital 108, Hanoi, Vietnam

Address for correspondence Mai Hong Son, MD, PhD, Department of Nuclear Medicine, Hospital 108, Hanoi, Vietnam (e-mail: alex.hong.son@gmail.com).

World J Nuclear Med 2023;22:226–233.

Abstract

Objective The aim of this study is to determine prognostic values of sequential ^{18}F -FDG PET/CT metabolic parameters in locally advanced esophageal squamous cell carcinoma (ESCC) patients treated with definitive chemoradiotherapy.

Materials and Methods Forty locally advanced ESCC patients treated with definitive chemoradiotherapy (dCRT) who received pre-treatment ^{18}F -FDG PET/CT (PET1) and 3-months post-treatment ^{18}F -FDG PET/CT (PET2) were enrolled in the prospective study. ^{18}F -FDG PET parameters of the primary tumor including maximum and mean standardized uptake values (SUVmax, SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated on PET delineated primary tumor. Using Kaplan-Meier curves to estimated overall survival (OS), progression-free survival (PFS), and local-regional control (LRC). Cox regression analysis was performed to find significant prognostic factors for survival.

Results With a median follow-up of 13.5 months, the 4-year OS, PFS, and LRC rates were 67.3%, 52.6%, and 53.4% respectively. Patients with MTV $2 > 5.7$ had lower OS, PFS, and LRC rates than the lower MTV 2 group ($p < 0.05$). Univariate Cox regression analysis showed that MTV2 was a significant prognostic factor for OS, PFS, and LRC ($p < 0.05$).

Conclusion MTV parameter of sequential ^{18}F -FDG PET/CT could be used as a prognostic factor for OS, PFS, and LRC in locally advanced ESCC patients treated with dCRT.

Keywords

- ▶ ^{18}F -FDG PET/CT
- ▶ sequential metabolic parameter
- ▶ predictive value
- ▶ definitive chemoradiotherapy
- ▶ esophageal squamous cell carcinoma

Introduction

Esophageal cancer is one of the most common cancers in the world.¹ Despite recent improvements in treatment modalities,

overall survival (OS) remains poor. Upper-third esophageal carcinoma including cervical and upper thoracic tumor represents approximately 10% of esophageal cancer.² Surgery is considered a primary treatment modality for the middle and lower third esophageal tumors.³ Meanwhile, radical surgery meets challenges in upper-third esophageal tumors due to the high risk of complications and death.

* These authors contributed equally to the study and retain the first authorship.

Squamous cell carcinoma histologically accounts for over 90% of upper-third esophageal carcinoma that is sensitive to radio-chemotherapy. Therefore, definitive chemoradiation therapy (dCRT) is a standard treatment with improving survival in comparison with surgery or radiation therapy alone.⁴⁻⁷

It has been proved that ^{18}F -fluoro-2-deoxy-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) has an important role in staging, radiotherapy planning, restaging, and follow-up of esophageal cancer.^{8,9} Esophageal tumors can be evaluated by endoscopy, ultrasound endoscopy, computed tomography, and ^{18}F -FDG PET/CT.¹⁰ Metabolic changes measured by ^{18}F -FDG PET occur earlier than morphological changes. Therefore, ^{18}F -FDG PET/CT can detect malignant tumor, recurrent or metastasis diseases earlier than conventional imaging.¹¹⁻¹³

Recently, the prognostic role of ^{18}F -FDG PET/CT has been increasingly investigated. Several papers have shown that pretreatment quantitative parameters derived from ^{18}F -FDG PET/CT such as maximum standardized uptake value SUVmax, total lesion glycolysis (TLG), and metabolic tumor volume (MTV) were independent prognostic factors for treatment outcomes.¹⁴⁻¹⁶ Besides that, sequential ^{18}F -FDG PET/CT after dCRT seems to be a more promising tool in prognosis of outcomes. Some studies proved that sequential ^{18}F -FDG PET/CT was helpful to evaluate the treatment outcomes as well as making decision to guide personalized therapy such as SUVs and tumor burden parameters.^{17,18} Moreover, sequential SUVmax, TLG, and MTV were used as the primary parameter of quantitative ^{18}F -FDG PET/CT in prognosis outcome in few studies.¹⁹⁻²¹ A study of Kim et al showed that relative change of SUVmean and MTV is related to local-regional recurrences and distant metastases after radiation therapy.²² Li et al reported that sequential TLG was more reliable than MTV in prognosis for outcome after dCRT.¹⁷ However, the actual prognostic role of sequential ^{18}F -FDG PET/CT parameters still being debated.²³

In this study, we aimed to assess the potential value of sequential SUVs parameters, MTV, and TLG in prognosis of local-regional control (LRC), progression-free survival (PFS), and OS in upper-third esophageal squamous cell carcinoma (ESCC) patients after dCRT.

Materials and Methods

Patients' Population

A prospective study with 60 consecutive upper-third ESCC patients registered from May 2017 to November 2021 at 108 Military Central Hospital. The inclusion criteria were (1) upper third esophageal tumor, (2) squamous cell carcinoma confirmed by endoscopic biopsy, (3) stage II or III by American Joint Committee on Cancer 7th, and (4) Eastern Cooperative Oncology Group performance status: 0 to 2, (5) age more than or equal to 18 years. The exclusion criteria were (1) other serious comorbidities, (2) previous radiation or chemotherapy, (3) abdominal lymph-node metastasis, and (4) insufficient follow-up data (20 patients). Forty patients underwent dCRT and had two ^{18}F -FDG PET/CT image series.

Whole body ^{18}F -FDG PET/CT was performed within 2 weeks before dCRT, then sequential PET scan was repeated after treatment 12 weeks. The primary endpoint was OS and secondary endpoints were PFS and locoregional-free survival. This study was approved by the Institutional Review Board of Hospital 108 (No 127/QD-VNC). Written informed consent was obtained from all patients before registration.

^{18}F -FDG PET/CT Procedure

All patients underwent whole-body ^{18}F -FDG PET/CT in the Department of Nuclear Medicine, the Hospital 108. PET/CT scan was performed, using GE Discovery 710 (GE Healthcare, Milwaukee, Wisconsin, United States), according to the European Association of Nuclear Medicine guidelines, version 2.0.²⁴ Patients should be fasted at least 4 hours, and blood sugar was measured before injection of ^{18}F -FDG. The PET/CT study schedule was postponed when glucose level higher than 11 mmol/L (about 200 mg/dL). Afterward, the patients rested in the waiting room before intravenous injection of 2.5 MBq/kg body weight ($\pm 10\%$) of ^{18}F -FDG. The parameters of the low dose CT scan were as follows: 120 kVp, modulated milliampere-seconds (mAs), the helical slice thickness of 3.75 mm, and 0.5 s/rotation. PET images were reconstructed using an iterative algorithm with attenuation correction with CT.

Quantitative ^{18}F -FDG Metabolic Assessment

^{18}F -FDG PET/CT images were evaluated by two experienced nuclear medicine physicians and the consensus was reached in each case. The volume of interest was set manually to exclude adjacent physiological ^{18}F -FDG-avid structures on attenuation-corrected PET images at the AW workstation version 4.7 (GE Healthcare, Milwaukee, Wisconsin, United States). Then, the region of interest in the esophageal lesions was assessed with reference to patient's symptoms, endoscopy, and CT imaging. The tumor volume was determined by iterative adaptive threshold segmentation provided by vendor (PETVCAR software, GE Healthcare). The iterative algorithm used a slope gradient vector algorithm which found a threshold value that separated the tumor from the background tissue by weighting the SUV max value within the bounding box by a "w" weight factor (where $0 \leq w \leq 1$ with default value of 0.5). The tumor border was then semiautomatically contoured and MTV was obtained as tumor volume (**Supplement Fig. 1**). SUVmax and SUVmean were defined as the maximum and mean value of SUV in MTV. TLG was calculated as SUVmean multiplied by MTV. All ^{18}F -FDG PET/CT derived parameters were computed by PETVCAR software (version 4.7, GE Healthcare, Milwaukee, Wisconsin, United States). ^{18}F -FDG-avid lesions were defined as uptake above that of mediastinal blood pool activity, or above the background activity. In case of noncomplete response, both PET scans would be co-registered and the sequential parameters were identified by semiautomatic delineation method based on the original location of primary tumor with manual adjustment of esophagitis and physiological high uptake regions. Tumor's quantitative parameters were SUVmax, SUVmean, MTV, and TLG computed by PETVCAR software

Table 1 General characteristic of esophageal squamous cell carcinoma patients

Clinical characteristics	No. of patients (n = 40)	Percent (%)
Age (mean ± SD)	58.0 ± 7.6	
Sex		
Male	40	100
Tumor site		
Cervical	12	30.0
Thorax	28	70.0
Pathology		
Highly differentiated (G1)	2	5.0
Moderately differentiated (G2)	20	50.0
Poorly differentiated (G3)	17	42.5
Unclassified (GX)	1	2.5
T stage		
T1b	2	5.0
T2	3	7.5
T3	35	87.5
N stage		
N0	4	10.0
N1	23	57.5
N2	11	27.5
N3	2	5.0
TNM stage		
IIA	1	2.5
IIB	5	12.5
IIIA	22	55.5
IIIB	10	25.0
IIIC	2	5.0
Chemotherapy regimen		
Cisplatin/5-FU	6	15.0
Paclitaxel/carboplatin	34	85.0
Interval time between the end of dCRT and PET2 (months)	3.3 ± 0.2	
Follow-up median (months)	13.5 (6–50)	

Abbreviations: 5-FU, fluorouracil; dCRT, definitive chemoradiation therapy; PET2, positron emission tomography2; SD, standard deviation.

(version 4.7, GE Healthcare, Milwaukee, Wisconsin, United States).²⁵ Derived parameters were collected on pretreatment ¹⁸F-FDG PET/CT: SUVmax1, SUVmean1, MTV1, TLG1, and posttreatment: SUVmax2, SUVmean2, MTV2, TLG2 (→ **Supplement Fig. 2**).

Chemoradiation Therapy

dCRT was approved by tumor board in oncology institute of the Hospital 108. Gross tumor volumes were identified by the combination of contrast-enhanced CT simulation and ¹⁸F-FDG PET/CT. Intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost technique delivers a total dose of 60 Gy to the primary tumor and active lymph nodes, 50.4 Gy to regional lymph nodes in 28 fractions. Chemotherapy was administered with cisplatin 75 mg/m² day 1 plus fluorouracil (5-FU) 750 mg/m² from day 1 to 4 (weeks 1, 5, 9, 13) or paclitaxel 50 mg/m² plus carboplatin AUC2 (days 1, 8, 15, 22, 29).

Follow-Up

Sequential ¹⁸F-FDG PET/CT was assessed 3 months after completion of dCRT. Patients were followed up every 3 months

with clinical examination, esophageal endoscopy, and chest-abdominal CT. After 2 years, the patients underwent follow-up every 6 months. OS was defined as the time from the start of dCRT to death of any cause or the last day of clinical follow-up. PFS was defined as the time from the beginning of dCRT to the day of disease progression or death of any cause or the last day of clinical follow-up. LRC was the length of time from the start of treatment to the day of progression or recurrence within irradiated field.

Statistical Analysis

Commercial software packages were used for statistical analysis (SPSS v.22.0, IBM Corp). Categorical values were compared using the chi-square test or Fisher’s exact test. Continuous variables were compared using paired Student’s t-test with normal distribution or Mann–Whitney U test with abnormal distribution.²⁶ Estimating LRC, PFS, and OS was analyzed by using Kaplan–Meier methods. Cox regression analysis was used to determine the prognostic parameters for OS, PFS, and LRC. Mean value of FDG PET/CT parameters were used to identify cutoff values for OS, PFS, and LRC. The statistical significance was set at p-value less than 0.05.²⁷

Table 2 Changes of tumor parameters between initial and sequential ¹⁸F-FDG PET/CT

	PET 1			PET 2			p-Value
	Mean	Median	Range	Mean	Median	Range	
SUVmax	14.5	13.6	2.9–34.1	5.5	4.0	1.6–20.9	0.000 ^a
SUVmean	6.7	7.0	2.3–15.1	3.1	2.9	1.3–8.7	0.000 ^a
MTV	18.6	13.7	0.9–55.3	5.7	1.7	0.1–32.5	0.000 ^a
TLG	151.3	96.3	2.2–778.4	27.4	5.0	0.2–283.8	0.000 ^a

Abbreviations: ¹⁸F-FDG PET/CT, ¹⁸F-flouro-2-deoxy-glucose positron emission tomography/computed tomography; MTV, metabolic tumor volume; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis.

^aMann–Whitney U test.

Results

Patients’ Characteristics

The general characteristics of patients was summarized in ►Table 1. Forty consecutive patients, 100% male with mean age of 58, were included in the study. The majority of patients 34/40 (85.5%) were classified with stage III. Paclitaxel/carboplatin regimen was administered in 85% of patients. During the median follow-up of 13.5 months, 10 patients were death. Causes of death were tumor progression (7 patients), lung metastasis (2 patients), and esophageal perforation (1 patient).

The Prognostic Value of Sequential ¹⁸F-FDG PET/CT Parameters for LRC, PFS, OS

The tumor metabolic parameters derived from PET 1 and PET 2 were showed in ►Table 2. The 4-year OS, PFS, and LRC rate were 67.3, 52.6, and 53.4%, respectively (►Fig. 1). On Cox regression univariate analysis, MTV2 was a significant prognosis factor for OS (heart rate [HR]=1.07, *p*=0.022), PFS (HR = 1.05, *p* = 0.045), and LRC (HR = 1.07, *p* = 0.005) (►Table 3). The median OS, PFS, and LRC of patients with MTV2 of 5.7 mL or higher were 13, 7, and 8 months, respectively, which were significantly worse than that of patients with MTV2 less than 5.7 mL (*p* < 0.05; ►Fig. 2).

Discussion

Definitive chemoradiation is the first-choice treatment of inoperable esophageal cancer, especially in patients with squamous cell carcinoma. Despite the improvement in radiotherapy techniques such as IMRT, the outcomes of ESCC patients remain poor with 5-year OS around 25 to 31%.^{28,29} Tumor stage and lymph node involvement are two well-known prognostic factors of esophageal cancer.^{30,31} Other clinical factors could impact on OS including malnutrition, comorbidities, and low socioeconomic status.³² Our study showed clinical staging, tumor histological grading, and chemo regimen were not significant prognostic factors for survival (*p* > 0.05). The primary tumor and nodal status of patients in our study could not be confirmed by pathology that might lead to inaccurate in assessment of clinical staging and histological grading. Our result is in line with previous study that showed comparable OS between carboplatin/paclitaxel and cisplatin/5-FU as dCRT in esophageal cancer patients.³³

Prognostic role of ¹⁸F-FDG PET/CT has been investigated in recent studies. But which parameters derived from ¹⁸F-FDG PET/CT should be used as prognostic factors for survival in esophageal cancer is still matter of debate. Our study reported that posttreatment MTV (MTV 2) was a significant factor in prognosis of LRC, PFS, and OS by univariate Cox

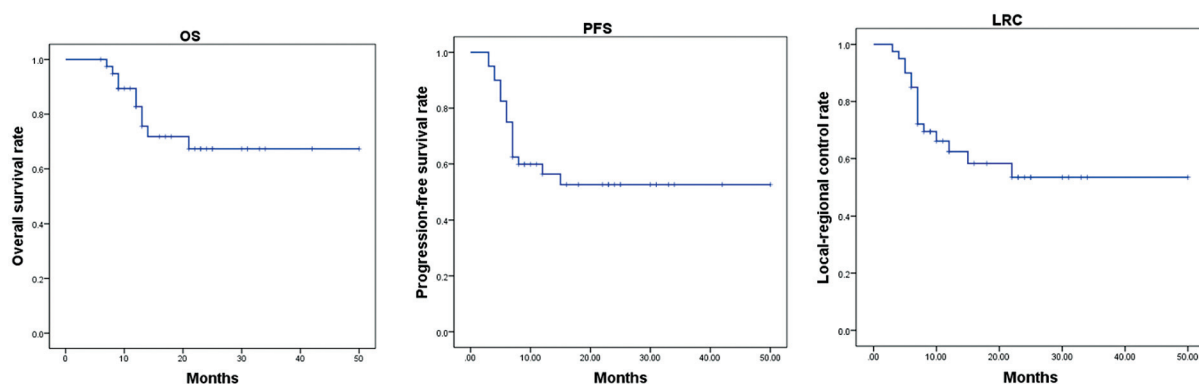


Fig. 1 Kaplan–Meier curve for survival. LRC, locoregional recurrence; OS, overall survival; PFS, progression-free survival.

Table 3 Univariate Cox regression analysis for OS, PFS, and LRC in ESCC patients treated with dCRT

Parameters	OS			PFS			LRC		
	HR	95% CI	p-Value	HR	95% CI	p-Value	HR	95% CI	p-Value
Stage III/ II	28.37	0.31–25,959.87	0.336	3.47	0.46–26.12	0.228	1.37	0.48–3.95	0.560
Pathology G3/G1-2	2.06	0.58–7.31	0.263	1.55	0.60–4.02	0.368	0.83	0.30–2.34	0.728
Chemo CF/PC	2.79	0.72–10.86	0.138	1.68	0.55–5.12	0.358	1.33	0.38–4.68	0.655
SUVmax1	1.06	0.97–1.15	0.182	1.05	0.98–1.12	0.148	1.05	0.98–1.13	1.146
SUVmean 1	1.32	0.99–1.53	0.061	1.12	0.95–1.31	0.173	1.12	0.93–1.34	0.234
MTV 1	1.04	1.00–1.07	0.044*	1.02	0.99–1.05	0.193	1.02	0.98–1.05	0.408
TLG 1	1.00	1.00–1.01	0.060	1.00	1.00–1.01	0.237	1.00	1.00–1.01	0.322
SUVmax 2	1.12	0.98–1.27	0.094	1.08	1.0–1.18	0.070	1.12	1.02–1.22	0.013*
SUVmean 2	1.28	0.87–1.88	0.209	1.26	0.99–1.59	0.057	1.39	1.10–1.77	0.006*
MTV 2	1.07	1.01–1.13	0.022*	1.05	1.00–1.09	0.045*	1.07	1.02–1.12	0.005*
TLG 2	1.01	0.99–1.02	0.092	1.00	0.99–1.01	0.258	1.01	1.00–1.01	0.181

Abbreviations: CI, confidence interval; dCRT, definitive chemoradiation therapy; ESCC, esophageal squamous cell carcinoma; HR, heart rate; LRC, locoregional recurrence; MTV1, metabolic tumor volume1; OS, overall survival; PFS, progression-free survival; SUVmax 1, maximum standardized uptake value 1; TLG 1, total lesion glycolysis 1. *denotes significant difference.

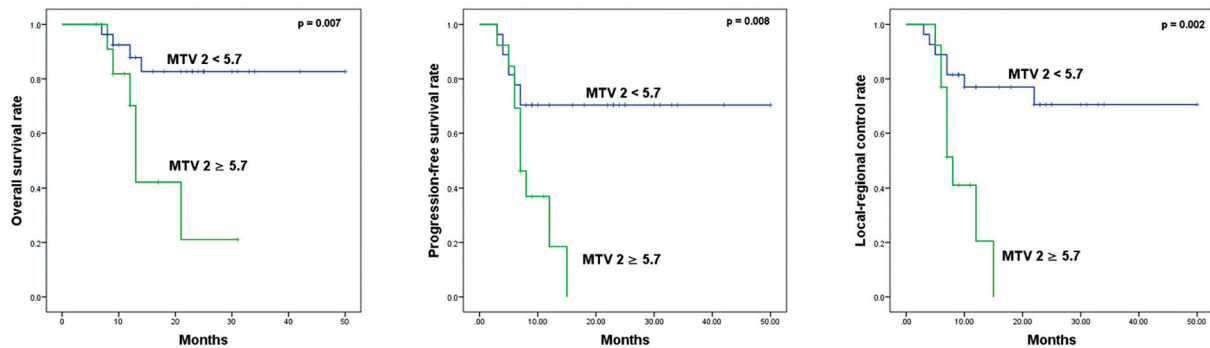


Fig. 2 Kaplan–Meier curves for overall survival, progression-free survival, and local–regional control according to metabolic tumor volume 2 more than or equal to 5.7 and less than 5.7 mL. MTV 2, metabolic tumor volume 2.

regression analysis. Patients with MTV 2 more than 5.7 had worse OS, PFS, and LRC than that with MTV 2 of 5.7 or less ($p < 0.05$). MTV reflects the active metabolic state of the whole tumor and it is considered to be a comprehensive parameter in prediction of treatment response and prognosis. Hence, this parameter may represent the shrinkage of the viable tumor portion after chemo and/or radiation therapy. Some studies showed that MTV was better than SUVmax that represents a small part of tumor in prognosis of esophageal cancer.^{20,34–36} MTV2 shows the volume of metabolic lesion that remains after therapy and it may have value in prognosis of treatment response and outcome. Moreover, Tamandl et al founded that MTV2 with cutoff value of 5.8 could predict pathological complete response that correlated to OS.³⁷ Prognostic role of other ¹⁸F-FDG PET/CT parameters was mentioned in some studies. The optimal cutoff prognostic

value of SUVs, MTV, and TLG varied across studies because they may depend on histopathologic features, necrosis, heterogeneity of tumor, and methods of segmentation.^{38–40} Li et al reported that SUVmax 2, TNM, and length of primary tumor were independent prognostic factors for OS.¹⁷ This study used 40% of SUVmax as the lower threshold for MTV calculations, which included primary tumor and lymph node with highest SUVmax. In our study, MTV was determined by iterative adaptive threshold method that has been proved more accurate than fix threshold method.⁴¹

MTV and TLG are emerging new parameters, and they seem to have more promising results in prognosis than other parameters.^{17,19,21,22,42} The prognostic value of these parameters for treatment outcome was approved in laryngeal carcinoma and nonsmall cell lung cancer in recent studies.^{43,44} A systemic review of Cremonesi et al showed

Table 4 Sequential ¹⁸F-FDG PET/CT parameters and clinical outcomes among studies

Author, year	No. of patients/Study style	Pathology	Protocol	Prognostic factors	Cutoff value	Outcomes
Chen et al ⁴⁶ 2015	34 Prospective	SCC	dCRT	MTV 1 ΔSUVmax	21 mL 70%	PFS PFS, LRC
Li et al ¹⁷ 2015	160 Retrospective	SCC	dCRT	MTV 1 TLG 1 ΔSUVmax	22 mL 170 67%	OS OS OS
Kim et al ⁴² 2016	53 Retrospective	AC	CRT + Sur	ΔTLG ΔMTV ΔSUVmax	44.4% 25.5% 23.5%	OS
Li et al ²¹ 2019	134 Retrospective	SCC	dCRT	MTV 1 TLG1 SUVmax 2 TLG 2	10.5 mL 59.8 7.8 44.3	OS OS OS OS
Kim et al ²² 2019	21 Retrospective	SCC	CRT +/- Sur	ΔMTV ΔSUVmean	1.14 35%	LRC DM

Abbreviations: dCRT, definitive chemoradiation therapy; DM, distant metastasis; LRC, locoregional recurrence; MTV1, metabolic tumor volume 1; OS, overall survival; PFS, progression-free survival; PFS, progression-free survival; SCC, squamous cell carcinoma; Sur, surgery; SUVmax 1, maximum standardized uptake value 1; TLG 1, total lesion glycolysis 1.

that there were not constant correlation between sequential ¹⁸F-FDG PET/CT parameters and clinical outcomes among studies (→Table 4).⁴⁵ Therefore, further research is needed with uniform protocol and method of analysis to assess prognostic value of sequential ¹⁸F-FDG PET/CT.

Several studies demonstrated that pretreatment ¹⁸F-FDG PET/CT parameters such as SUVmax, MTV, and TLG of primary tumor were independent prognostic factors for treatment outcomes.^{14-16,21,46} Our result showed only MTV 1 had prognostic value for OS in univariate analysis. Posttreatment residual lesion is the part of the primary tumor that is resistant to chemoradiotherapy and might directly cause recurrent or metastasis.²² Therefore, sequential ¹⁸F-FDG PET/CT might be more promising tool than pretreatment ¹⁸F-FDG PET/CT in prognosis of outcomes. The prognostic role of sequential ¹⁸F-FDG PET/CT in our study was in line with several studies.^{21,22,42}

Our study had some limitations. First, this is a single-center study that may had inherent biases. Second, metabolic parameters of sequential FDG PET/CT do not accurately reflect the effectiveness of treatment due to postradiation inflammation. In addition, only parameters of the primary tumor were evaluated, while the outcomes of ESCC actually correlated to both tumor and metastatic lymph node parameters. Moreover, the number of patient enrollment is limited and the time of follow-up is less than 5 years. Those explain why we did not find any independent prognostic factor for survival when performing multivariate Cox regression analysis in our study.

Conclusion

Our study suggests that posttreatment MTV (MTV2) with a cutoff value of 5.7 mL can be used to prognose clinical outcomes in locally advanced ESCC patients treated with dCRT. These findings need to be validated by further studies with a larger cohort of patients.

Authors' Contribution

Le Ngoc Ha, Nguyen Dinh Chau, and Mai Hong Son were involved in writing of the manuscript. Nguyen Dinh Chau helped in data collection. Mai Hong Son, Le Ngoc Ha, and Nguyen Dinh Chau helped in editing and submission of the manuscript. All the authors contributed equally to this paper.

Ethical Approval

This study was approved by the Institutional Review Board of Central Military Hospital 108 (approval No. 165/QD-V108).

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

No funding.

Conflict of Interest

None declared.

Acknowledgment

We thank to all nuclear medicine staffs, radiation oncology staffs, and Dr. Andrea Skanjneti for their contribution.

References

- Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(03): 209-249
- Ding X, Zhang J, Li B, et al. A meta-analysis of lymph node metastasis rate for patients with thoracic oesophageal cancer and its implication in delineation of clinical target volume for radiation therapy. *Br J Radiol* 2012;85(1019):e1110-e1119

- 3 Ajani JA, Barthelemy JS, Bentrem DJ, et al; National Comprehensive Cancer Network. Esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011;9(08):830–887
- 4 Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 2012;19(01):68–74
- 5 Burmeister BH, Dickie G, Smithers BM, Hodge R, Morton K. Thirty-four patients with carcinoma of the cervical esophagus treated with chemoradiation therapy. *Arch Otolaryngol Head Neck Surg* 2000;126(02):205–208
- 6 Kato K, Muro K, Minashi K, et al; Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (JCOG) Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). *Int J Radiat Oncol Biol Phys* 2011;81(03):684–690
- 7 van Hagen P, Hulshof MCCM, van Lanschot JJB, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366(22):2074–2084
- 8 Kumar P, Damle NA, Bal C. Role of F18-FDG PET/CT in the staging and restaging of esophageal cancer: a comparison with CECT. *Indian J Surg Oncol* 2011;2(04):343–350
- 9 Muijs CT, Beukema JC, Pruim J, et al. A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer. *Radiother Oncol* 2010;97(02):165–171
- 10 Bruzzi JF, Munden RF, Truong MT, et al. PET/CT of esophageal cancer: its role in clinical management. *Radiographics* 2007;27(06):1635–1652
- 11 Gopal A, Xi Y, Subramaniam RM, Pinho DF. Intratumoral metabolic heterogeneity and other quantitative ¹⁸F-FDG PET/CT parameters for prognosis prediction in esophageal cancer. *Radiol Imaging Cancer* 2020;3(01):e200022
- 12 Han S, Kim YJ, Woo S, Suh CH, Lee JJ. Prognostic value of volumetric parameters of pretreatment 18F-FDG PET/CT in esophageal cancer: a systematic review and meta-analysis. *Clin Nucl Med* 2018;43(12):887–894
- 13 Shum WY, Ding HJ, Liang JA, Yen KY, Chen SW, Kao CH. Use of pretreatment metabolic tumor volumes on PET-CT to predict the survival of patients with squamous cell carcinoma of esophagus treated by curative surgery. *Anticancer Res* 2012;32(09):4163–4168
- 14 Atsumi K, Nakamura K, Abe K, et al. Prediction of outcome with FDG-PET in definitive chemoradiotherapy for esophageal cancer. *J Radiat Res (Tokyo)* 2013;54(05):890–898
- 15 Rizk NP, Tang L, Adusumilli PS, et al. Predictive value of initial PET-SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. *J Thorac Oncol* 2009;4(07):875–879
- 16 Suzuki A, Xiao L, Hayashi Y, et al. Prognostic significance of baseline positron emission tomography and importance of clinical complete response in patients with esophageal or gastroesophageal junction cancer treated with definitive chemoradiotherapy. *Cancer* 2011;117(21):4823–4833
- 17 Li Y, Zschaek S, Lin Q, Chen S, Chen L, Wu H. Metabolic parameters of sequential 18F-FDG PET/CT predict overall survival of esophageal cancer patients treated with (chemo-) radiation. *Radiat Oncol* 2019;14(01):35
- 18 Wieder HA, Ott K, Lordick F, et al. Prediction of tumor response by FDG-PET: comparison of the accuracy of single and sequential studies in patients with adenocarcinomas of the esophagogastric junction. *Eur J Nucl Med Mol Imaging* 2007;34(12):1925–1932
- 19 Chang S, Koo PJ, Kwak JJ, Kim SJ. Changes in total lesion glycolysis evaluated by repeated F-18 FDG PET/CT as prognostic factor in locally advanced esophageal cancer patients treated with preoperative chemoradiotherapy. *Oncology* 2016;90(02):97–102
- 20 Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C. Prognostic value of 18F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology. *Eur J Nucl Med Mol Imaging* 2011;38(07):1191–1202
- 21 Li Y, Lin Q, Wang L, et al. Application of sequential (18)F-FDG PET/CT scans for concurrent chemoradiotherapy of non-surgical squamous cell esophageal carcinoma. *J BUON* 2014;19(02):517–523
- 22 Kim N, Cho H, Yun M, Park KR, Lee CG. Prognostic values of mid-radiotherapy ¹⁸F-FDG PET/CT in patients with esophageal cancer. *Radiat Oncol* 2019;14(01):27
- 23 Omloo JMT, van Heijl M, Hoekstra OS, van Berge Henegouwen MI, van Lanschot JJB, Sloof GW. FDG-PET parameters as prognostic factor in esophageal cancer patients: a review. *Ann Surg Oncol* 2011;18(12):3338–3352
- 24 Boellaard R, Delgado-Bolton R, Oyen WJG, et al; European Association of Nuclear Medicine (EANM) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015;42(02):328–354
- 25 Larson SM, Erdi Y, Akhurst T, et al. Tumor treatment response based on visual and quantitative changes in global tumor glycolysis using PET-FDG imaging. The visual response score and the change in total lesion glycolysis. *Clin Positron Imaging* 1999;2(03):159–171
- 26 Milenović Ž Application of Mann-Whitney U test in research of professional training of primary school teachers. *Metod Obz Horiz* 2011;6(01):73–79
- 27 Grabowski B. “P < 0.05” might not mean what you think: American Statistical Association clarifies p values. *J Natl Cancer Inst* 2016;108(08):d1w194
- 28 Cooper JS, Guo MD, Herskovic A, et al; Radiation Therapy Oncology Group. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999;281(17):1623–1627
- 29 Shi A, Liao Z, Allen PK, et al. Long-term survival and toxicity outcomes of intensity modulated radiation therapy for the treatment of esophageal cancer: a large single-institutional cohort study. *Adv Radiat Oncol* 2017;2(03):316–324
- 30 Bouvier AM, Binquet C, Gagnaire A, Jouve JL, Faivre J, Bedenne L. Management and prognosis of esophageal cancers: has progress been made? *Eur J Cancer* 2006;42(02):228–233
- 31 Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 2008;247(02):365–371
- 32 Vendrely V, Launay V, Najah H, Smith D, Collet D, Gronnier C. Prognostic factors in esophageal cancer treated with curative intent. *Dig Liver Dis* 2018;50(10):991–996
- 33 Honing J, Smit JK, Muijs CT, et al. A comparison of carboplatin and paclitaxel with cisplatin and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. *Ann Oncol* 2014;25(03):638–643
- 34 Cervino AR, Evangelista L, Alfieri R, et al. Positron emission tomography/computed tomography and esophageal cancer in the clinical practice: how does it affect the prognosis? *J Cancer Res Ther* 2012;8(04):619–625
- 35 Hatt M, Majdoub M, Vallières M, et al. 18F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015;56(01):38–44
- 36 Nakajo M, Jinguji M, Nakabeppu Y, et al. Texture analysis of ¹⁸F-FDG PET/CT to predict tumour response and prognosis of patients with esophageal cancer treated by chemoradiotherapy. *Eur J Nucl Med Mol Imaging* 2017;44(02):206–214
- 37 Tamandl D, Fueger B, Haug A, et al. A diagnostic algorithm that combines quantitative 18F-FDG PET parameters and contrast-

- enhanced CT improves posttherapeutic locoregional restaging and prognostication of survival in patients with esophageal cancer. *Clin Nucl Med* 2019;44(01):e13–e21
- 38 Adams MC, Turkington TG, Wilson JM, Wong TZ. A systematic review of the factors affecting accuracy of SUV measurements. *AJR Am J Roentgenol* 2010;195(02):310–320
- 39 Koopman D, Jager PL, Slump CH, Knollemans S, van Dalen JA. SUV variability in EARL-accredited conventional and digital PET. *EJNMMI Res* 2019;9(01):106
- 40 Nahmias C, Wahl LM. Reproducibility of standardized uptake value measurements determined by ¹⁸F-FDG PET in malignant tumors. *J Nucl Med* 2008;49(11):1804–1808
- 41 Tamal M. Intensity threshold based solid tumour segmentation method for Positron Emission Tomography (PET) images: a review. *Heliyon* 2020;6(10):e05267
- 42 Kim SJ, Koo PJ, Chang S. Predictive value of repeated F-18 FDG PET/CT parameters changes during preoperative chemoradiotherapy to predict pathologic response and overall survival in locally advanced esophageal adenocarcinoma patients. *Cancer Chemother Pharmacol* 2016;77(04):723–731
- 43 Al-Ibraheem A, Abdulkadir AS, Al-Adhami D, et al. The prognostic and diagnostic value of [¹⁸F]FDG PET/CT in untreated laryngeal carcinoma. *J Clin Med* 2023;12(10):3514
- 44 Berkowitz AC, Halmos B, Cheng H, Huntzinger C, Ohri N. FDG-PET metrics in advanced non-small cell lung cancer (NSCLC): a review and meta-analysis. *Clin Transl Imaging*. Doi: 10.1007/s40336-023-00542-y
- 45 Cremonesi M, Garibaldi C, Timmerman R, et al. Interim ¹⁸F-FDG-PET/CT during chemo-radiotherapy in the management of oesophageal cancer patients. A systematic review. *Radiother Oncol* 2017;125(02):200–212
- 46 Chen H, Li Y, Wu H, et al. 3'-deoxy-3'-[¹⁸F]-fluorothymidine PET/CT in early determination of prognosis in patients with esophageal squamous cell cancer: comparison with [¹⁸F]-FDG PET/CT. *Strahlenther Onkol* 2015;191(02):141–152