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Original Article

Value of sequential 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in prediction of the overall survival of esophageal cancer patients treated with chemoradiotherapy

Yimin Li[1*], Qin Lin[1*], Zuoming Luo[2], Long Zhao[2], Luchao Zhu[1], Long Sun[2], Hua Wu[2]

[1]Department of Radiation Oncology, The Xiamen First Affiliated Hospital of Xiamen University, Xiamen 361003, P. R. China; [2]Department of Nuclear Medicine, The Xiamen First Affiliated Hospital of Xiamen University, Xiamen 361003, P. R. China. [*]Equal contributors.

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Abstract: This study is to investigate the value of the metabolic parameters measured by sequential FDG PET/CT in predicting the overall survival of patients with esophageal squamous cell carcinoma (ESCC). A total of 160 patients who were newly diagnosed as ESCC patients and treated with chemoradiotherapy were included in this study. The FDG PET/CT was carried out prior to radiotherapy (PET1), when the cumulative dose of radiotherapy reached 50 Gy (PET2), at the end of radiotherapy (PET3) and 1 month after radiotherapy (PET4). The max of the standard uptake value (SUVmax) of the primary tumor, the metabolic tumor volume (MTV) and the total lesion glycolisis (TLG) prior to treatment were measured. The correlation of the measured parameters and the derived parameters of SUVmax with the overall survival was analyzed. The relatively reduced percentage of the SUVmax of PET3 and PET4 to the SUVmax of PET1 and PET2, had predictive value for the overall survival. The area under researcher operation curve (ROC) was between 0.62 and 0.73 ($P < 0.01$). The MTV and TLG prior to treatment might be used to predict the overall survival, and the area under ROC were both 0.69 ($P < 0.001$). Sequential FDG PET/CT scanning is useful to predict the overall survival of chemoradiotherapy for ESCC. The metabolic parameters and the derived parameters of FDG PET/CT have predictive values for overall survival.

Keywords: Esophageal cancer, FDG PET/CT, survival analysis

Introduction

The incidence and mortality of esophageal carcinoma rank eighth and sixth, respectively, among the common malignancies worldwide [1]. Surgery is an important means for the treatment of esophageal cancer. However, more than 70% of the patients diagnosed with esophageal cancer lost the chance of surgery because of advanced stage cancer or complications that are not suitable for surgery. For these patients, chemoradiotherapy is the main treatment method. Some researchers drafted the guidelines for clinical staging of gastric cancer, hoping to predict the effect of non operation therapy on esophageal cancer patients [2]. However, the imaging diagnosis methods for staging are mainly CT and barium meal, which are prone to be affected by edema and scar fibrosis. As a result, the predictive ability of the guidelines is relatively poor.

As the development and the application of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), the role of molecular imaging in evaluating responses of malignant tumor to treatments has been investigated by many research groups [3-5]. However, the staging, the curative effect evaluation and the prognosis of esophageal cancer are still controversial [6, 7]. It is reported that FDG PET/CT could be used to predict the prognosis of esophageal carcinoma [8, 9]. However, these researches were conducted in esophageal ade-

nocarcinoma patients who received surgical treatment. The application of FDG PET/CT in predicting the prognosis of esophageal cancer without surgical treatment is less studied.

The purpose of this study is to evaluate the dynamic changes of the FDG uptake parameters in patients with esophageal squamous cell carcinoma (ESCC) prior to, in the middle of and after chemoradiotherapy, by using sequential FDG PET/CT scanning. The role of sequential FDG PET/CT scanning in predicting overall survival of ESCC patients who were treated with chemoradiotherapy but not surgery was investigated.

Materials and methods

Patients

From October 2008 to June 2013, 162 patients were diagnosed with histologically confirmed primary ESCC. Among them, 160 patients were enrolled in this retrospective study, and 2 were not included due to patient disapproval. Tumor stage and disease grade were classified according to the 6th edition of the International Union Against Cancer. Clinical data of patients were shown in **Table 1**. The inclusion criteria of patients was as follows: voluntary participations who were over 18 years old; patients who did not receive surgery, radiotherapy, chemotherapy or targeted therapy before; patients who were diagnosed with ESCC; patients who were without severe dysfunction in hematopoietic function, heart, lung, liver or kidney and without immunodeficiency; patients who were with the expected survival time over 3 months. Prior written informed consent was obtained from all patients enrolled before undergoing the examination. The study protocol was approved by the ethical committee.

Radiotherapy

Radiation therapy was carried out on the lesion area as follows. Gross tumor volume of primary tumor (GTV-t) was determined according to the high metabolic region of esophagus shown by PET/CT and avoid the blood vessel by enhanced CT. Gross tumor volume of lymph node (GTV-nd) include the metastatic lymph node detected by CT, PET/CT and physical palpation. Clinical tumor volume of primary tumor (CTV-t) was 4 cm proximal and distal margins, with a 0.5 cm radial margin added to the gross tumor volume. CTV-nd was delineated including the GTV-nd and the corresponding lymph node drainage area based on different locations of the primary lesion, all CTVs should avoid the anatomical barrier. Planning target volume (PTV) in combination with the areas extending 0.5 cm from GTV-t, GTV-nd, CTV-t and CTV-nd formed GTV-t-P, GTV-nd-P, CTV-t-P and CTV-nd-P. The total irradiation dose of both 95% GTV-t-P and GTV-nd-P was 60 Gy and external radiation was applied in 30-33 fractions of 1.8 Gy-2.0 Gy over the course of 5 days a week. The total irradiation of CTV-t-P and CTV-nd-P was 50 Gy and external radiation was applied in 25-28 fractions of 1.8 Gy-2.0 Gy over the course of 5 days a week.

Chemotherapy

Patients older than 70 years underwent radical radiotherapy. Patients less than 70 years with phase II esophageal cancer or more advanced stage esophageal cancer were treated with concurrent chemotherapy based on cisplatin. Chemotherapy was performed 1 day prior to the start of radiotherapy. The concurrent chemotherapy regimen for most patients consisted of infusion of cisplatin (25 mg/m^2/d, d1-d3 and d29-d31) and paclitaxel (135 mg/m^2/d, d1 and d29). The concurrent chemotherapy regimen for other patients consisted of cisplatin (25 mg/m^2/d, d1-d3 and d29-d31) and 5-FU (500 mg/m^2/d, d1 and d29).

FDG PET/CT scan

The patients enrolled received 4 times of FDG PET/CT scanning during the whole treatment process. The time points were as follows: one week prior to chemoradiotherapy, the time point at which GTVs-P cumulative dose of radiotherapy reached 50 Gy, the end of radiotherapy and one month after radiotherapy. Whole body imaging technology was performed at the first scan, and chest imaging was conducted during the other three scans. The 4 scans were named as PET1, PET2, PET3 and PET4 according to the time sequence (**Figure 1**).

The standard procedure of PET/CT scan (GE Discovery STE; GE Healthcare) was performed. The drugs used in 18F-FDG were produced by our cyclotron facility (General Electric Company, Fairfield, Connecticu, USA), with the radiochem-

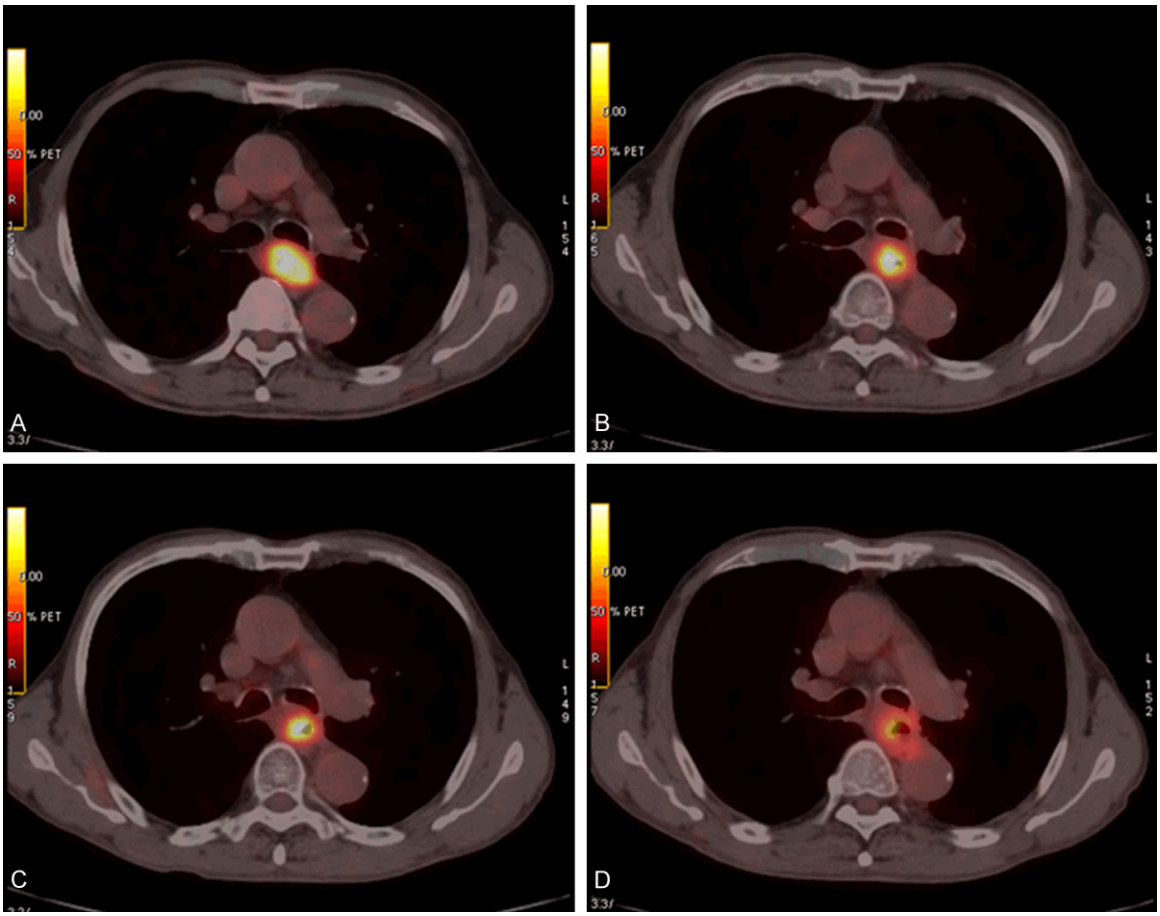

Figure 1. Changes of the SUVmax of primary tumor during radiotherapy. The SUVmax value of the esophagus primary tumor was 12.5, 11.8, 9.8, and 6.4 at the time of before treatment (A), when the cumulative dose of radiotherapy reached 50 Gy (B), at the end of radiotherapy (C) and one month after radiotherapy (D).

ical purity of more than 95%. Whole body imaging was carried out over an area of from the head to the proximal femur, and the local imaging was from the head to epigastrium. PET scanning was performed with a scan-bed acquisition time of about 15 minutes. The data were reconstructed iteratively for image fusion by application of CT attenuation correction. The coronal, sagittal and axial fusion images of CT, PET and PET/CT together with 3D mode were acquired.

All the images were reviewed by at least two experienced radiologists, who were unaware of the diagnosis and clinical data. Combined with CT images, the limited radioactive concentration area of esophageal lesions and neck, thorax and abdomen was identified as the region of interest (ROI). The edge of ROI was the line that was 40% SUVmax (max of the standard uptake value) larger than the primary area defined automatically by the ROI software (Advantage work station, version 4.3, GE, USA). And the site of heart and other physiological high uptake areas were avoided by visual adjustment. The values of the primary lesion and the lesion adjacent metastatic lymph nodes of PET1, PET2, PET3 and PET4 were recorded as follow, SUVmax, SUVmean (the average value of SUV), MTV (the metabolic tumor volume), TLG (Total Lesion Glycolysis, TLG). The calculation formula of TLG was: TLG = SUVmean × MTV. When the lymphnode beyond the primary tumor and the metastatic lymph node was more than 3 cm, the larger of SUVmax was recorded as SUVmax for statistical analysis, and the sum of two lesions was used for MTV and TLG statistical analysis. If the esophageal lesions disappeared completely after radiotherapy, the SUV was measured according to the anatomic position of primary lesions. No

Table 1. Clinical data of patients (n = 160)

Clinical features	Evaluable patients (%)
Age	
Mean 62 ± 10 years	--
Range (42-90 years)	--
Sex	
Male	126 (79%)
Female	34 (21%)
Pathological grading	
Well differentiated (G1)	16 (10%)
Moderately differentiated (G2)	99 (62%)
Poorly differentiated (G3)	23 (14%)
Undifferentiated (G4)	6 (4%)
Undetermined (Gx)	16 (10%)
Primary tumor	
Cervical	13 (8%)
Upper thoracic	49 (30%)
Mid-thoracic	70 (44%)
Lower thoracic	22 (14%)
Multi-site origin	6 (4%)
T stage	
T2	8 (5%)
T3	58 (36%)
T4	94 (59%)
N stage	
N0	75 (47%)
N1	85 (53%)
M stage	
M0	157 (98%)
M1b	3 (2%)
Concurrent chemotherapy	
No	63 (39.4%)
Yes	97 (60.6%)
Therapy methods	
Conventional radiotherapy	28 (18%)
Intensity modulated radiotherapy	132 (82%)

Note: --, not indicated.

MTV data during and after radiotherapy was recorded due to the interference of radioactive inflammation.

Statistical analysis

Survival was calculated from the beginning of chemoradiotherapy to the date of death or most recent follow-up. The data was expressed as mean ± standard deviation (SD). All statistical analyses were performed by using the SPSS 17.0. One-way ANOVA was used to compare SUVmaxs, MTV and TLG prior to treatment and the Mann-Whitney nonparametric test was used to analyze the derived parameters from PET/CT scanning at different time in different survival groups. The receiver operating characteristic curve (ROC) was used to find the optimal prediction threshold. Log-Rank test was performed to compare the difference in overall survival. The Kaplan-Meier method analysis was performed to analyze the independent prognostic factors for survival. $P < 0.05$ was considered as statistically significant.

Results

Clinical data of patients

Table 1 summarized the clinical pathological characteristics of the patients. All the patients were squamous cell carcinoma. The follow-up was carried out to January 1, 2014. The 160 patients were all successfully followed up and the median follow-up time was 10 months (2-55 months). There were 85 cases that died of tumor-related diseases and 75 cases were live at the deadline of follow up.

Dynamic changes of FDG SUV in the process of radiotherapy

SUVmax was measured at different time points and compared with each other. **Figure 1** shows the axial images of one case at 4 time points. The numbers of cases completed the scan of PET1, PET2, PET3, PET4 were 160, 130, 131, and 114. With the increase of irradiation dose, the average SUVmax of primary tumor decreased. The average SUVmax of PET1, PET2, PET3 and PET4 was 14.2 ± 6.5, 6.6 ± 2.9, 5.7 ± 5.4 and 4.6 ± 4. The differences between the SUVmax of PET1 and that of PET2, PET3 and PET4 were significant ($P < 0.001$). There was significant difference between the SUVmax of PET2 and PET4 ($P = 0.001$). No significant difference was found between the SUVmax of PET2 and PET3 ($P = 0.291$).

Correlation of SUVmax with curative effect and prognosis

To investigate the correlation of SUVmax with curative effect and prognosis, one-way ANOVA was performed. According to death or not, the SUVmax of PET1, PET2, PET3 and PET4 was divided into the survival group and the death group. As shown in **Table 2**, there was no signifi-

Table 2. Differences in SUVmax of the 4 observation times between the survival group and the death group compared with one-way ANOVA analysis

	SUVmax (PET1)		SUVmax (PET2)		SUVmax (PET3)		SUVmax (PET4)	
	survival	death	survival	death	survival	death	survival	death
Cases	75	85	65	65	68	63	62	52
Mean	13.9	14.6	6.2	7.1	5.1	6.4	3.7	5.7
Standard deviation	7.1	5.8	2.9	2.8	2.0	2.6	1.8	3.3
F	0.413		3.59		10.26		16.99	
P	0.522		0.061		0.002		0.000	

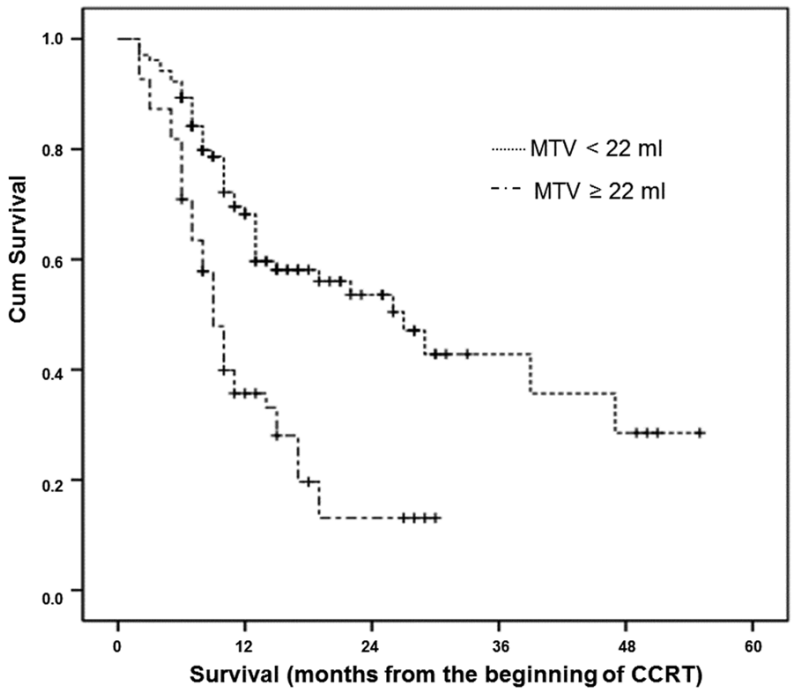

Figure 2. Survival of patients with the MTV of PET1 less than 22 ml was significantly greater than that with MTV more than 22 ml. The corresponding sensitivity and specificity were 0.49 and 0.84, respectively ($P = 0.000$).

cant difference between the survival and the death group in SUVmax of PET1 and PET2. Meanwhile, there were significant differences in SUVmax of PET3 ($P = 0.002$) and PET4 ($P = 0.000$). The ROC curve was generated to determine the cutoff value of SUVmax at which the result of sensitivity calculate specificity were highest. The SUVmax of PET1 had no prediction value. The SUVmax of PET2, PET3 and PET4 might be used for prediction, with the *P* value of 0.028, 0.003 and 0.000, and with the area under the curve of 0.611, 0.651 and 0.718. The optimal prediction threshold of the SUVmax of PET2 was 4.25 (sensitivity, 0.89; specificity, 0.36). The survival of the patients with SUVmax less than 4.25 was significantly higher than that with SUVmax more than 4.25. The median survival time of patients with SUVmax less than 4.25 was 40.5 months (95% CI, 31.6-49.4 months) and that of with SUVmax more than 4.25 was 20.3 months (95% CI, 16.2-24.5 months). And the difference between them was significant ($P < 0.001$). The optimal prediction threshold of PET3 SUVmax was 6.2 (sensitivity, 0.49; specificity 0.75). The survival of the patients with SUVmax less than 6.2 was significantly higher than that with SUVmax more than 6.2. Kaplan-Meier survival analysis show the median survival time of patients with SUVmax of PET3 less than 6.2 and more than 6.2 was 31.5 months (95% CI, CI 25.8-37.2 months) and 16.7 months (95% CI, 11.1-22.3 month). And the difference between them was significant, with $P < 0.001$. The optimal prediction threshold of PET4 SUVmax was 5 (sensitivity, 0.52; specificity 0.85). The survival of patients with SUVmax less than 5 was significantly higher than that with SUVmax more than 5. The median survival time of the two groups was 34.3 months (95% CI, 28.3-40.3 months) and 12.3 months (95% CI, 8.7-15.9 months), and $P < 0.001$.

Value of MTV and TLG in the prediction of overall survival

MTV and TLG of PET1 were divided into the survival group and the death group. Means of MTV prior to treatment were 14.0 cm^3 (survival group) and 26.0 cm^3 (death group) and the cor-

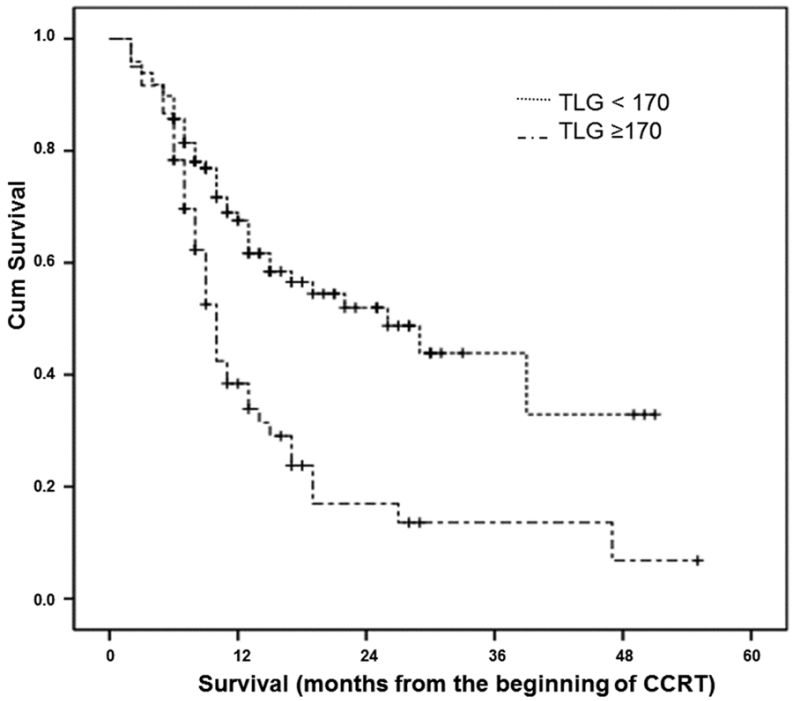

Figure 3. Survival of patients with the TLG of PET1 less than 170 was significantly greater than that with TLG more than 170. The corresponding sensitivity and specificity were 0.52 and 0.78, respectively (P = 0.000).

Table 3. The derided parameters of SUVmax and their implications

Derided parameters	Implications
ΔS12	SUVmaxpet1-SUVmaxpet2
ΔS13	SUVmaxpet1-SUVmaxpet3
ΔS14	SUVmaxpet1-SUVmaxpet4
ΔS23	SUVmaxpet2-SUVmaxpet3
ΔS24	SUVmaxpet2-SUVmaxpet4
ΔS34	SUVmaxpet3-SUVmaxpet4
ΔR12	(SUVmaxpet1-SUVmaxpet2)/SUVmaxpet1
ΔR13	(SUVmaxpet1-SUVmaxpet3)/SUVmaxpet1
ΔR14	(SUVmaxpet1-SUVmaxpet4)/SUVmaxpet1
ΔR23	(SUVmaxpet2-SUVmaxpet3)/SUVmaxpet1
ΔR24	(SUVmaxpet2-SUVmaxpet4)/SUVmaxpet1
ΔR34	(SUVmaxpet3-SUVmaxpet4)/SUVmaxpet1

Note: SUVmaxpet1, SUVmaxpet2, SUVmaxpet3 and SUVmaxpet4 represent the SUVmax of FDG PET/CT scanning carried prior to radiotherapy, when the cumulative dose of radiotherapy reached 50 Gy, at the end of radiotherapy and 1 month after radiotherapy. SUVmax, max of the standard uptake value.

respondent data of TLG were 121.4 (survival group) and 225.8 (death group). One-way ANOVA analysis show there were statistically significant differences in the parameters of MTV and TLG between the survival and death groups (P < 0.001). The MTV and the TLG before radiotherapy both had predictive value, with P < 0.001, and the area under the curve were both 0.69, respectively. The optimal prediction threshold of MTV before radiotherapy was 22 ml (sensitivity, 0.49; specificity 0.84). Based on this threshold, the survival team with MTV before treatment lower than 22 ml was significantly higher than that with MTV more than 22 ml. Kaplan-Meier survival analysis show that median survival time of the two groups was 29.4 months (95% CI, 24.1-34.7 months) and 12.1 months (95% CI, 9.7-14.5 months) and P < 0.001 (**Figure 2**). Similarly, the optimal prediction threshold of TLG prior to radiotherapy was 170 (sensitivity, 0.52; specificity 0.79). Based on this threshold, the survival time with TLG before treatment lower than 170 were obviously higher than that of above 170. The median survival time of the two groups was 28.1 months (95% CI, 23.0-33.1 months) and 15.8 months (95% CI, 11.2-20.3 month) and P < 0.001 (**Figure 3**).

Value of the derived parameters from SUVmax

The derived parameters of SUVmax were shown in **Table 3**. Each derived parameters of the teams were grouped according to survival or death and was compared with Mann-Whitney nonparametric test. The absolute value of SUVmax change prior to treatment and one month after treatment (ΔR14) was found to have statistically significant differences between the survival and death groups (P = 0.04). ROC curve was gener-

ated to determine the optimal prediction threshold. The ROC curve showed that ΔR14 had predictive value (P = 0.04), and the area under the curve was 0.62. The cutoff is 0.67 (sensitivity and specificity was 0.63 and 0.58, respectively and the P value was 0.03) Based on this threshold, Kaplan-Meier survival analysis show the survival time of patients with ΔR14 more than 0.67 was obviously less than that with ΔR14 less than 0.67. The median survival time of the two groups were 31 months (95% CI, 23.7-38.3 months) and 15.8 months (95% CI, 11.3-20.3 months), P = 0.001. With the same method, the survival rate of patients with ΔR24 less than 0.10 was significantly greater than that with ΔR24 more than 0.10. The corresponding sensitivity and specificity was 0.66 and 0.61, respectively and the P-value was 0.014.

Discussion

In this study, we performed sequential FDG PET/CT scanning at 4 time points, and no similar study is reported. To avoid influence by artificial factors, ROI was determined by the combined methods of automatic delineation by software and removal of physiological uptake region by visual adjustment. When the irradiation dose reached 50 Gy and 60 Gy, the metabolic uptake at the site of the primary tumor significantly decreased and it was not obvious when compared with the surrounding tissue. In some cases, it was difficult to find the primary lesion after the treatment. The measurement accuracy of the software was greatly affected. Therefore, the MTV and TLG during and after treatment were not used for statistical analysis.

As calculated by ROC analysis, there were statistically significant difference in the SUVmax of PET2 and PET3 when they were grouped according to survival or died. This might be caused by the reasons that the cells those were easily killed were died after radical radiotherapy or concurrent 2 cycles of chemotherapy and the residual cells were relatively insensitive to radiotherapy or resistant to chemotherapy. The high SUV indicates that the activity of the highly resistant cells might be very strong, and they could easily lead to local failure or recurrence in a short time, thus resulting in increased mortality. In addition, the accelerated reproliferation of tumor cells in the late period might also lead to SUV increase. At present, the main treatment method for esophageal carcinoma that is not suitable for surgery is chemoradiotherapy; however, there is no recognized standard dose for radiotherapy during the chemoradiotherapy [10]. Our results may be helpful in determining the dose of radiotherapy. For patients with high SUVmax of PET3, the treatment efficacy may be improved through increasing the radiation dose or performing adjuvant chemotherapy. And, it is better to perform three-dimensional conformal or intensity-modulated radiotherapy. Additionally, the increase in SUVmax of PET3 might also be caused by increased inflammatory responses induced by esophageal ulcer [11]. Some researchers performed FDG PET/CT at an early time to evaluate the efficacy. For example, Lordick et al. [12] carried out FDG PET/CT 2 weeks after the start of neoadjuvant chemotherapy. In our study, the patients did not receive surgical treatment because of locally advanced esophageal carcinoma, surgical intolerant or disapproval to operation. Thus, early PET/CT screening was not performed.

The SUVmax of PET4 showed predictive value for survival. This indicates that the tumor might have subsided because of chemoradiotherapy induced inflammation and other factors one month after chemoradiotherapy. The residual tumor is easier to be detected by PET/CT at this time point. Consistently, other studies also showed similar results [13-15]. The SUVmax of PET4 could be used to predict overall survival, and there was statistically significant difference when they were grouped according to survival or died. Therefore, the derived parameters of ΔR14 and ΔR24 could also be used to predict overall survival. And the FDG PET/CT performed at this time point could reflect the real quantity of residual tumor, thus better predicting the survival [3]. Schmidt et al. [16] found that the SUVmax of the postoperative pathological reaction group was slightly high, and the SUVmax of the pathological reaction group decreased more significantly. Some research results were not consistent with our results [17, 18]. This inconsistency might be caused by the differences in sample size and treatment response rate.

Both of the MTV and TLG prior to treatment are considered to be the factors that can reflect the

volume and metabolism of solid tumors and are used more and more in survival prediction [19]. Shum et al. [20] found that the survival of patients with MTV more than 16 ml was poor. Hyun SH et al. [21] reported similar results that the MTV was an independent prognostic factor related to the TNM stage. Our results showed that the MTV before treatment was an independent prognostic factor for overall survival, suggesting that it might be used for predicting the overall survival of esophageal cancer patients treated with non operation therapy. By analyzing the ROC curve, we found that the optimal prediction threshold of MTV for overall survival was 22 ml.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hua Wu, Department of Nuclear Medicine, Xiamen First Affiliated Hospital of Xiamen University, 55, Zhenhai Road, Siming District, Xiamen 361003, P. R. China. Tel: 86-13559216164; Fax: 86-592-2139527; E-mail: xmliyimin@126.com

References

[1] Kamangar F, Dores GM and Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24: 2137-50.

[2] Esophageal Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health. Clinical staging criterion of non surgical esophageal cancer (draft). Chin J Radist Oncol 2010; 19: 179.

[3] Schöder H, Fury M, Lee N and Kraus D. PET monitoring of therapy response in head and neck squamous cell carcinoma. J Nucl Med 2009; 50 Suppl 1: 74S-88S.

[4] Kong FM, Frey KA, Quint LE, Ten Haken RK, Hayman JA, Kessler M, Chetty IJ, Normolle D, Eisbruch A and Lawrence TS. A pilot study of [18F] fluorodeoxyglucose positron emission tomography scans during and after radiation-based therapy in patients with non small-cell lung cancer. J Clin Oncol 2007; 25: 3116-23.

[5] Bussink J, Kaanders JH, van der Graaf WT and Oyen WJ. PET-CT for radiotherapy treatment planning and response monitoring in solid tumors. Nat Rev Clin Oncol 2011; 8: 233-42.

[6] Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D, Coosemans W, Ectors N, Haustermans K, Mortelmans L. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000; 18: 3202-10.

[7] Vali FS, Nagda S, Hall W, Sinacore J, Gao M, Lee SH, Hong R, Shoup M and Emami B. Comparison of standardized uptake value-based positron emission tomography and computed tomography target volumes in esophageal cancer patients undergoing radiotherapy. Int J Radiat Oncol Biol Phys 2010; 78: 1057-63.

[8] Zhu WQ, Yu JM, Sun XR. The prognostic value of metabolic tumor volume in FDG PET/CT evaluation of post-operative survival in patients with esophageal squamous cell cancer. Chin J Nucl Med 2011; 31: 378-81.

[9] Monjazeb AM, Riedlinger G, Aklilu M, Geisinger KR, Mishra G, Isom S, Clark P, Levine EA and Blackstock AW. Outcomes of patients with esophageal cancer staged with [18F] fluorodeoxyglucose positron emission tomography (FDG-PET): can postchemoradiotherapy FDG-PET predict the utility of resection? J Clin Oncol 2010; 28: 4714-21.

[10] Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA and Kelsen DP. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002; 20: 1167-74.

[11] Erasmus JJ, Munden RF, Truong MT. Preoperative chemo-radiation-induced ulceration in patients with esophageal cancer: a confounding factor in tumor response assessment in integrated computed tomographic-positron emission tomographic imaging. J Thorac Oncol 2006; 1: 478-86.

[12] Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, Lorenzen S, Schuster T, Wieder H, Herrmann K, Bredenkamp R, Höfler H, Fink U, Peschel C, Schwaiger M, Siewert JR. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol 2007; 8: 797-805.

[13] Levine EA, Farmer MR, Clark P, Mishra G, Ho C, Geisinger KR, Melin SA, Lovato J, Oaks T and Blackstock AW. Predictive value of 18-fluorodeoxy-glucose-positron emission tomography

(18F-FDG-PET) in the identification of responders to chemoradiation therapy for the treatment of locally advanced esophageal cancer. Ann Surg 2006; 243: 472-8.

[14] Javeri H, Xiao L, Rohren E, Lee JH, Liao Z, Hofstetter W, Maru D, Bhutani MS, Swisher SG, Macapinlac H, Wang X and Ajani JA. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastroesophageal adenocarcinoma. Cancer 2009; 115: 5184-92.

[15] Vallböhmer D, Hölscher AH, Dietlein M, Bollschweiler E, Baldus SE, Mönig SP, Metzger R, Schicha H and Schmidt M. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemoradiation in esophageal cancer. Ann Surg 2009; 250: 888-94.

[16] Schmidt M, Bollschweiler E, Dietlein M, Mönig SP, Kobe C, Vallböhmer D, Eschner W, Hölscher A, Schicha H. Mean and maximum standardized uptake values in [18F] FDG-PET for assessment of histopathological response in oesophageal squamous cell carcinoma or adenocarcinoma after radiochemotherapy. Eur J Nucl Med Mol Imaging 2009; 36: 735-44.

[17] Makino T, Doki Y, Miyata H, Yasuda T, Yamasaki M, Fujiwara Y, Takiguchi S, Higuchi I, Hatazawa J and Monden M. Use of (18) F-fluorodeoxyglucose-positron emission tomography to evaluate responses to neo-adjuvant chemotherapy for primary tumor and lymph node metastasis in esophageal squamous cell carcinoma. Surgery 2008; 144: 793-802.

[18] Roedl JB, Colen RR, Holalkere NS, Fischman AJ, Choi NC and Blake MA. Adenocarcinomas of the esophagus: response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. Comparison to histopathologic and clinical response evaluation. Radiother Oncol 2008; 89: 278-86.

[19] Roedl JB, Halpern EF, Colen RR, Sahani DV, Fischman AJ and Blake MA. Metabolic tumor width parameters as determined on PET/CT predict disease-free survival and treatment response in squamous cell carcinoma of the esophagus. Mol Imaging Biol 2009; 11: 54-60.

[20] Shum WY, Ding HJ, Liang JA, Yen KY, Chen SW and 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: 4163-8.

[21] Hyun SH, Choi JY, Shim YM, Kim K, Lee SJ, Cho YS, Lee JY, Lee KH and Kim BT. Prognostic value of metabolic tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography in patients with esophageal carcinoma. Ann Surg Oncol 2010; 17: 115-22.