RESEARCH ARTICLE

Pre-treatment Metabolic Tumor Volume and Total Lesion Glycolysis are Useful Prognostic Factors for Esophageal Squamous Cell Cancer Patients

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Abstract

Objectives: To study application of the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) with ^{18}F-FDG PET/CT for predicting prognosis of esophageal squamous cell cancer (ESC) patients. Methods: Eighty-six patients with ESC staged from I to IV were prospectively enrolled. Cisplatin-based chemoradiotherapy (CCRT) or palliative chemoradiotherapy were the main treatment methods and none received surgery. ^{18}F-FDG PET/CT scans were performed before the treatment. SUVmax, MTV, and TLG were measured for the primary esophageal lesion and regional lymph nodes. Receiver operating characteristic curves (ROCs) were generated to calculate the P value of the predictive ability and the optimal threshold. Results: MTV and TLG proved to be good indexes in the prediction of outcome for the ESC patients. An MTV value of 15.6 ml and a TLG value of 183.5 were optimal threshold to predict the overall survival (OS). The areas under the curve (AUC) for MTV and TLG were 0.74 and 0.70, respectively. Kaplan-Meier analysis showed an MTV less than 15.6 ml and a TLG less than 183.5 to indicate good media survival time (p value <0.05). In the stage III-IV patient group, MTV could better predict the OS ($P < 0.001$), with a sensitivity and specificity of 0.80 and 0.67, respectively. Conclusions: Pre-treatment MTV and TLG are useful prognostic factors in non-surgical ESC.

Keywords: ^{18}F deoxyglucose - positron emission tomography - esophageal SCC - chemoradiotherapy - survival analysis

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Introduction

Esophageal cancer is the 8th most common cancer worldwide, and ranks the 6th among the causes of deaths resulted from cancers (Jemal et al., 2011). East-Asia is an endemic region of esophageal squamous cancer (ESC). Although surgery remains the treatment of choice for ESC, more than 70% ESC patients lost the chance. For such patients, chemoradiotherapy becomes the alternative. As no postoperative pathological clue available, the prediction of the therapeutic effects and prognosis has to depend on morphological methods like CT and barium meal. However, the CT and barium meal are very susceptible to inflammation, scarring and edema, which make the results not reliable.

Compared with CT and esophageal barium meal, ^{18}F-FDG PET/CT can provide the metabolic information of the tumor and many studies indicate that ^{18}F-FDG PET/CT is useful in the prediction of the prognosis (Rizk et al., 2006; Omloo et al., 2008; Westerterp et al., 2008; Zhu and Sun, 2011). However, these studies are mainly focused on the operable patients and the most pathological type of subjects was adenocacinoma. Studies focused on non-operable ESC patients are very few. The aim of our study is to find whether SUVmax, MTV and TLG have the prognostic values in non-surgical ESC.

Materials and Methods

Patients

Eighty-six consecutive patients with pathologically proven ESC at our institution between October 2008 and June 2012 were enrolled. All patients had an ECOG score of 0-2 and none of them had been treated with chemotherapy or radiotherapy prior to this study. All of them did not receive operation. Before treatments, routine pretreatment evaluations were performed including physical examinations, complete blood counting, biochemical liver and kidney function tests, electrocardiography, pulmonary function determination, barium esophagography, contrast-enhanced chest CT, abdominal ultrasound or CT scans, and esophagogastroscopy with tumor biopsy. This study was approved by the review board in the first affiliated

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hospital of Xiamen university, China, and all patients had signed the informed consent.

PET imaging

Before imaging examination, the patients were instructed to fast for at least 6 h or overnight. The patients received an intravenous injection of 15 mCi (555 MBq) of FDG. Data were acquired 60 min after injection using an integrated PET-CT system (Biograph 16; Siemens Medical Solutions, Erlangen, Germany). Low-dose CT for attenuation correction was performed with the 16-slice multidetector CT component of the combined PET-CT, immediately followed by PET emission scan with a high-resolution lutetium oxyorthosilicate-based PET scanner in a three-dimensional (3D) mode. The transverse field of view was identical to the CT scan. The parameters were as follows: table feed, 15 mm/s; pitch, 1.5; tube voltage, 140 kV; and tube current, 170 mA. Images were reconstructed with a 2mm or 2.5mm slice thickness.

Measurement of PET parameters

All ^{18}F-FDG PET/CT images were interpreted by two experienced physicians. The region of intrest (ROI) was connection with the radioactive concentration in the esophageal anatomic area in three dimensions. Advantage Workstation 4.3 (GE Health care) was adopted to automatically calculate the max and the average uptake value of the ROI and named as SUVmax and SUVmean respectively. At the same time, the volume of SUV greater than 40%SUVmax of the primary tumor and adjacent lymph nodes was calculated by the Advantage Workstation 4.3 and the volume was defined as MTV (Bradley et al., 2004). If the metastatic lymph node was far from the primary tumor, the MTV of that lymph node would be calculated as a total MTV. TLG was defined as the MTV of the lesions multiplying SUVmean. The sixth-edition cancer staging system (the American Joint Committee) (Greene, 2002) was used to determine the disease stage.

Chemotherapy

The patients received one of the following three regimens: 1) cisplatin, 30 mg/ (m^2/day), from day 1 to 3, plus 5-fluorouracil as a continuous intravenous infusion at a dose of 500 mg/ (m^2/day), from day 1 to 5, for two or three 28-day cycles; 2) cisplatin 30 mg/m^2/day on day 1-3, plus paclitaxel 135 mg/m^2 on day 1 for two or three 28-day cycles; 3) If patients was more than 70 years old, chemotherapy was not considered. Recombinant human granulocyte colony-stimulating factor (Amoytop Pharmaceutical Co., Ltd., China) was used to assure completion of chemoradiotherapy if neutropenia occurred.

Radiotherapy

Image information of patients was obtained by CT-simulator (GE, USA). With the scope from the mastoid level to the lower border of the second lumbar vertebra, 5-mm-thick slice images were inquired, and then transferred to the radiotherapy planning system (Eclipse treatment planning system, Varian Medical Systems, US). 3D conformal radiotherapy or intensive-modulated radiotherapy was administered to all patients. The delineation of gross tumor volumes was based on CT, barium esophagography, endoscopic examination, and PET imaging. The clinical target volumes were 4cm proximal and distal margins, with a 0.5cm radial margin added to the gross tumor volume. The planning target volume encompassed a 0.8-cm proximal and distal margin and a 0.5-cm radial margin on the basis of clinical target volumes. At the same time, clinical target volumes were adjusted to avoid the anatomic structure. The maximum spinal cord dose was ≤ 4, 500 centigray (cGy). The volumetric percentage for the entire lungs received radiation dose of ≥ 2, 000 cGy was ≤ 30%. The average lung dose received was ≤1, 600 cGy. Radiotherapy was delivered by 4-6 fields using a 6 MV photon beam at the beginning of the first chemotherapy cycle. The prescription dose of gross tumor volume was 180-200 cGy per fraction to a total dose of 6000cGy within 6 weeks. The clinical tumor volume received 5000cGy in 5 weeks with the same fraction dose.

Following-up evaluation

Clinical following-up evaluation was performed from the end of treatment at a 3-month interval in the first two years and at a 6-month interval thereafter. Tumor response assessment included physical examination, blood and biochemical tests, barium swallow, CT scan and endoscopy. The following-up investigation was completed on January 1, 2013. Overall survival time was defined as the interval from the start of treatment to the date of death.

Statistical analyses

The statistical analysis was performed using SPSS17.0 software package. SUVmax, MTV and TLG data were expressed as mean ± standard deviation (SD). One-way ANOVA was used to compare the average. ROC (receiver operating characteristics) curve was adopted to determine the optimal threshold. The Kaplan-Meier method was used to estimate the survival function. The difference in survival rate between groups was tested for significance using the log-rank test. All tests were two-sided, and *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

In this study, 86 ESC patients were enrolled. Median age of the patients is 61y (range 42-88y) (Table 1). Primary site of the tumor are as follow: cervical sites, 2 cases; upper thoracic sites, 28 cases; middle thoracic sites, 37 cases; lower thoracic sites, 12 cases; and multicenter sites, 2 cases (Table 1). Median follow up is duration of 12 months (range 7 to 45 months) (Table 1).

^{18}F-FDG PET/CT parameters

The mean pre-treatment MTV and TLG was 22.6 ± 19.7ml and 186.6 ± 187.1, respectively. When age, gender were used as group factors, there were no statistical significance in SUVmax, MTV and TLG. When T stage and tumor length were considered as the group factor, the difference was statistical significant. When OS was defined as the group factor, there was still statistical

Table 1. Characteristics of Patients

Characteristics		Number of patients
Age (years)	< 65	54
	≥ 65	32
	median	61
	Range	42-88
Gender	Male	64
	Female	22
T stages	T1	2
	T2	13
	T3	29
	T4	42
N stages	N0	22
	N1	64
Sites	Cervical	7
	Upper thoracic	28
	Middle thoracic	37
	Lower thoracic	12
	Multicenter	2
ECOG*	0-1	68
	2	18

*ECOG performance status

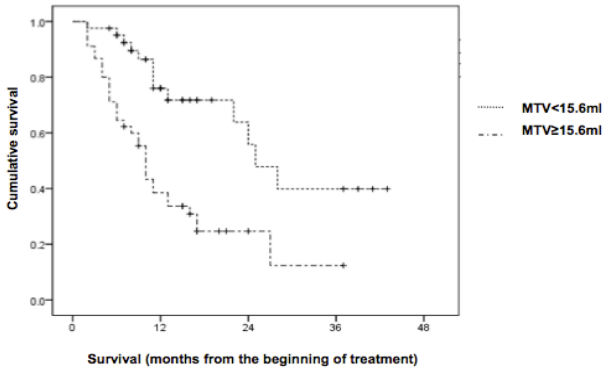

Figure 1. The Kaplan-Meier Survival Probability Analysis Shows A Statistically Significant Difference in OS in Relation to MTV (log-rank test, $P < 0.05$)

significance for both MTV and TLG but not for SUVmax (Table 2).

ROC was used to determine the optimal threshold (Hellwig et al., 2007). The value with the minimal false-negative rate (FNR) plus false-positive rate (FPR) was selected as the optimal cutoff. According to this principle, 15.6 ml of MTV and 183.5 of TLG were worked out as the optimal threshold values. Kaplan-Meier method show that patients group with MTV >15.6 or TLG >183.5 had a significantly good survival time (27.6 m vs. 13.9 m $P <$

Table 3. ROC Curve Results and Kaplan-Meier Survival Analysis by Group Factor of Optimal Cutoff

	ROC curve analysis		Kaplan-Meier survival analysis stated by death or not		
Parameters	AUC	*P* value	Cutoff	*P*	MST (m)
SUVmax	0.491	0.883	N/A	N/A	N/A
MTV	0.736	<0.001	15.6 ml	<0.001	27.6 VS 13.9
TLG	0.699	0.001	183.5	0.001	24.5 VS 13.4
Site	0.557	0.366	N/A	N/A	N/A
Age	0.504	0.952	N/A	N/A	N/A
Gender	0.541	0.511	N/A	N/A	N/A

AUC, Area under the curve; Cutoff, Optimal cutoff of the ROC; MST, Median Survival Time; N/A, ROC cannot get the optimal cutoff and Kaplan-Meier was not applied

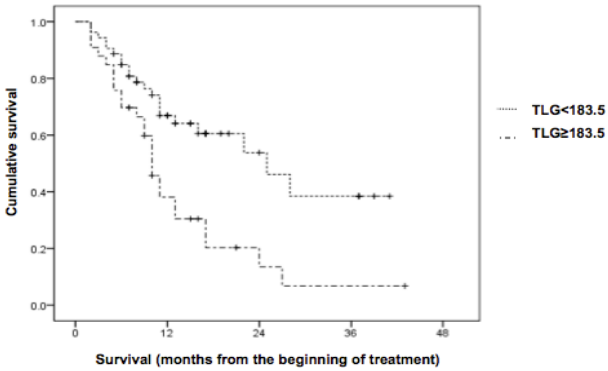

Figure 2. The Kaplan-Meier Survival Probability Analysis Shows a Statistically Significant Difference in OS in Relation to TLG (log-rank test, $P < 0.05$)

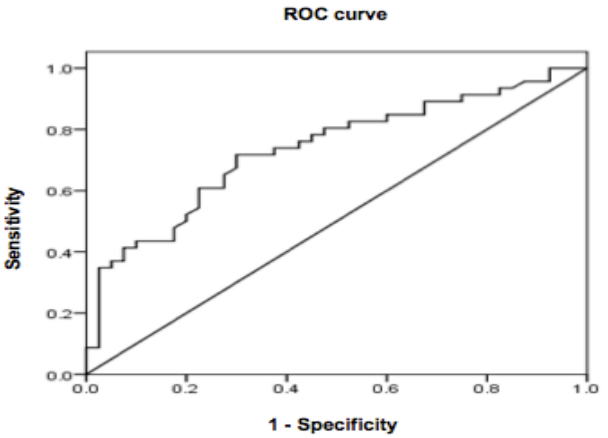

Figure 3. The ROC of MTV in Relation to OS (Test Value, $P < 0.001$). AUC, 0.74. 95%CI, 0.63-0.84

Table 2. Comparison of SUV-based PET/CT Parameters of Primary Tumor and Adjacent Nodes in Group of Clinical Informations and Death or not (One-Way ANOVA)

Items		SUVmax	*P*	MTV	*P*	TLG	*P*
Age (years)	< 65 (Pts = 54)	13.8 ± 8.2	> 0.05	25.8 ± 22.0	> 0.05	211.6 ± 212.7	> 0.05
	≥ 65 (Pts = 32)	13.8 ± 6.2		17.2 ± 14.0		144.4 ± 125.2	
Gender	Female (Pts = 22)	16.1 ± 8.0	> 0.05	19.8 ± 22.1	> 0.05	167 ± 134.1	> 0.05
	Male (Pts = 64)	13.0 ± 7.2		23.5 ± 19.0		193.4 ± 202.6	
T stages	1-2 (Pts =18)	10.3 ± 8.6	< 0.05	8.8 ± 6.7	< 0.05	52.0 ± 62.4	< 0.05
	3-4 (Pts = 68)	14.7 ± 7.0		26.3 ± 20.4		222.2 ± 192.7	
Lengths	< 5cm (Pts = 35)	11.3 ± 8.3	< 0.05	15.7 ± 19.7	< 0.05	98.7 ± 125.4	< 0.05
	≥ 5cm (Pts = 51)	15.4 ± 6.4		27.4 ± 18.4		247.0 ± 199.2	
Survival or death	survival (Pts = 40)	14.7 ± 9.8	> 0.05	14.7 ± 12.1	< 0.05	124.7 ± 113.6	< 0.05
	death (Pts = 46)	13.0 ± 4.7		29.5 ± 22.5		240.5 ± 220.3	

0.05, and 24.5m vs 13.4, both $p < 0.05$) (Figure 1, Figure 2, Table 3). ROC curve cannot find an optimal threshold with statistically significant in SUVmax, primary tumor site, age and gender by group factor of death or not and the Kaplan-Meier survival analysis cannot be used in such situation.

Discussion

Currently, prognostic judgment of non-surgical ESC is usually based on the maximum tumor diameter and volume as measured by CT. However, esophageal tumor usually has an irregular shape and is often accompanied with inflammation, necrosis and edema, it is difficult for CT to measure the true size of the tumor and the true tumor load accurately. PET/CT is a molecular imaging tool which can reflect the metabolic characteristics of a tumor and has more probability to give the real biological features. Therefore, it has been widely used in the prediction of response in various tumor including ESC. However, which parameters should be chosen is still not sure.

Many studies reported encouraging outcomes in using SUVmax or the decrease SUVmax to evaluate the prognosis of ESC (Rizk et al., 2006; Ma et al., 2013), while some studies also reported negative outcomes in terms of the prognostic value of the pre-treatment SUVmax (Hong et al., 2005; Klaeser et al., 2009). Our findings suggest that the pre-treatment SUVmax did not significantly correlate with patient prognosis. This may be due to some reasons: 1) SUVmax of FDG-PET/CT only represents the highest level of the glucose metabolism in the tumor tissue, whether the glucose metabolism truly represents the tumor biological characteristics in terms of therapeutic sensitivity or vulnerability to metastasis has not been established. 2) The variability of SUVmax is relatively large (Weber et al., 1999), which may lead to big uncertainty about the outcome.

Nowadays, MTV and TLG have been more and more used to evaluate the tumor reaction in therapy (Su and Ari, 2012). The same research can also be seen in ESC (Roedl et al., 2008; Hyun et al., 2010).

However, the subjects of the studies above mostly concentrated on the patients with adenocarcinoma and operation was the main treatment method. Our study focus on the subjects of squamous carcinoma and all the subject did not receive operation. The results of our study imply that compared with the SUVmax before treatment, MTV and TLG are prognostic factor for OS. It can reflect the prognosis of non-surgical ESC patients, which is consistent with the finding of Hyun et al. (2008; 2010).

We thought that MTV has better prognostic ability in our study maybe due to some reasons bellow. One is that MTV not only provides the metabolic information about the tumor but also could delegate the tumor volume size. It can reflect the real tumor burden. It is apparently superior to the simple anatomical information in prognostic prediction. Second is that our MTV prediction threshold was 15.6ml. If this volume was converted into a spherical lesion, the corresponding diameter is 3.10 cm, close to 3 cm which is recognized as a easy controllable tumor diameter. TLG was came from the MTV multiply by SUVmean of the lesion. Large TLG value means more tumor tissure in glycolysis and therefore entails more hypoxic cells which may lead to poor local control rates.

Concurrent chemoradiotherapy has been the standard treatment modality for inoperable EC (Herskovic et al., 1992; Cooper et al., 1999). Three dimension radiotherapy may give more benefit to survival (Shen et al., 2012). But there are many dispute in the radiation dosage and the combined medicine (Cooper et al., 1999). Therefore, to our study, patients who have a higher MTV or TLG may need to receive further treatment, including the use of increased radiation dose or targeted drugs like cetuximab, vascular endothelial growth inhibitor and some other molecular targeted drugs which may improve the survival.

In conclusion, the present study suggests that MTV and TLG as parameters of ^{18}F-FDG PET/CT are important prognostic factor for survival, and that MTV has a better prediction ability of survival than that of SUVmax for primary tumor in patients with non-surgical ESC. Patient care may be optimized by the volumetric parameter of ^{18}F-FDG PET/CT for the new prognostic stratification on TNM stage. Of course, validation of the prognostic utility of this promising functional biomarker derived from ^{18}F-FDG PET/CT need additional prospective and random studies with a larger numbers of patients.

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