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ORIGINAL ARTICLE

Application of sequential ^{18}F-FDG PET/CT scans for concurrent chemoradiotherapy of non-surgical squamous cell esophageal carcinoma

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Summary

Purpose: *To explore the values of sequential ^{18}F-FDG PET/CT scanning in patients with non-surgical esophageal squamous cell carcinoma (ESCC) who received concurrent chemoradiotherapy (CCRT).*

Methods: *Twenty-eight patients with pathologically confirmed stage I-IV ESCC and who received definitive CCRT were prospectively enrolled into this trial. The ^{18}F-FDG PET/CT scans were performed four times. The maximum standardized uptake values (SUVmax) of each scanning were named as SUVmaxpet1, SUVmaxpet2, SUVmaxpet3, and SUVmaxpet4, respectively. The tumor volume with SUV greater than 40% of SUVmax was named as metabolic tumor volume (MTV). Follow-up investigation of patients was performed to record progression-free survival (PFS), relapse-free survival (RFS), and overall survival time (OS).*

Results: *The average value of MTV before treatment is 19.3 ml. The average value of SUVmax at four time points was 13.0 ± 7.4, 6.4 ± 3.2, 4.7 ± 1.9, and 3.4 ±1.8, respectively. Median follow-up time was 18.5 months (range 5-40). There was statistically significant difference in ΔR14 ((SUVmaxpet1-SUVmaxpet4) / SUVmaxpet1). Multivariate Cox regression survival analysis indicated that the MTV was an independent prognostic factor for PFS and RFS (HR = 1.13 and 1.14, respectively) before treatment.*

Conclusion: *In CCRT of non-surgical ESCC, MTV before treatment could independently predict OS survival. SUVmaxpet2, SUVmaxpet3, and SUVmaxpet4 could predict RFS. Patients with reductions of SUVmaxpet4 less than 75% had a poor PFS, RFS, and OS.*

Key words: *concurrent chemoradiotherapy, esophageal carcinoma, ^{18}F deoxyglucose, positron emission tomography, survival*

Introduction

Esophageal cancer ranks eighth in tumor incidence and sixth in mortality worldwide [1]. Surgical operation is an important means for the treatment of esophageal carcinomas. However, more than 70% of esophageal cancer patients are at mid-or advanced disease stages when first diagnosed. These patients may lose the chance of surgical operation probably due to operation contraindications. Radiotherapy and chemotherapy are the main methods for treating such patients. Since there are no postoperative pathological data in such cases, it is not suitable to predict the efficacy of treatment of these patients with UICC/AJCC staging [2].

^{18}F-FDG PET/CT, a unique combination of the anatomical CT imaging and the functionally metabolic PET imaging, has been widely applied in the staging and prediction of treatment efficacy of esophageal cancer [3,4]. ^{18}F-FDG PET/CT has functional imaging advantage compared with CT, and some studies have revealed better predictive results for the prognosis of esophageal cancer [5,6]. However, these studies are mainly focused on patients with esophageal cancer who could be

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treated with surgical operation, especially on patients with adenocarcinoma. The effect of ^{18}F-FDG PET/CT on the prediction of squamous cell carcinoma patients who can not be subjected to surgical operation is rarely reported. And, it also remains controversial which types of parameters should be used to predict the treatment efficacy with ^{18}F-FDG PET/CT.

In this study, ESCC patients were subjected to ^{18}F-FDG PET/CT scanning at four time points: before radiotherapy, during radiotherapy, immediately after radiotherapy, and one month after radiotherapy. The parameters used in each scanning and the treatment efficacy and long-term follow-up effects were evaluated.

Methods

Patient information

A total of 28 patients with ESCC were enrolled. The study plan was approved by the ethics committee of Xiamen University, and prior written informed consent was obtained from each patient. Inclusion criteria included: biopsy-confirmed squamous cell carcinoma before treatment; expected survival time more than 3 months; patients unable to be subjected to surgical operation after surgical consultation or refusing to undergo operation; ECOG performance status 0-2; incomplete obstruction of the esophagus; and no hematogeneous metastasis. Clinical staging was based on the AJCC (6th Edn, 2002). General patient and disease characteristics are shown in Table 1.

^{18}F-FDG PET/CT

GE Discovery STE PET/CT scanner (GE, USA) was used in the study. The ^{18}F-FDG was provided by Min'nan PET Center, with radiochemical purity of > 95%. The imaging range included areas from vertex to the proximal femur. Blood glucose, height, and weight of patients were examined before imaging. All patients underwent fasting for 4-6 h before intravenous injection of ^{18}F-FDG, with a dose of 5.55 MBq/kg. After injection, the patients rested quietly for 40 min. 120 kV of tube voltage and 120 mA of tube current were applied in 16-layered spiral CT transmission scanning, and the thickness of each layer was 3.3 mm. The PET data collection lasted 2 min for each bed position, and with 6-7 beds, the total acquisition time was about 15 min. CT was applied for attenuation correction. Data were iteratively reconstructed to obtain coronal, sagittal, axial CT, PET, PET/CT fusion image and 3D image, respectively.

Data processing of PET imaging

The limited and radioactive concentrated area in the esophagus was targeted as the region of interest. Advantage Workstation 4.3 (GE, USA) software was used in this study. The workstation could automatically calculate the MTV, which included the volume of the primary tumor with size greater than 40% of the SUVmax before radiotherapy and chemotherapy and the volume of the biggest adjacent lymph node. The workstation could also automatically calculate SUVmax. If the number of lymph node metastasis with high metabolism was greater than 2, the total value of the primary tumor and the biggest metabolic lymph node was defined as MTV [7]. The measuring methods of SUVmaxpet2, SUVmaxpet3, and SUVmaxpet4 were performed according to the measurement of SUVmaxpet1. However, if there was complete tumor regression, the data were measured at the anatomical location of tumor before its disappearance. The name and meaning of each obtained metabolic parameter and derived parameters were shown in Table 2.

Table 1. Patient and disease characteristics

Characteristics	*N (%)*
Age (years)	
< 65	22 (78.6)
≥ 65	6 (21.4)
Median	59
Range	46 - 80
Gender	
Male	18 (64.3)
Female	10 (35.7)
Grade of differentiation	
Undifferentiated	2 (7.1)
Poorly differentiated	6 (21.4)
Moderately differentiated	16 (57.1)
Well differentiated	4 (14.3)
T stage	
T1	1 (3.6)
T2	5 (17.9)
T3	17 (60.7)
T4	5 (17.9)
N stage	
N0	10 (35.7)
N1	18 (64.3)
TNM stage	
I	6 (21.4)
II	8 (28.6)
III	11 (39.3)
IV	3 (10.7)
Primary tumor site	
Neck	2 (7.1)
Upper thoracic	10 (35.7)
Middle thoracic	14 (50.0)
Lower thoracic	2 (7.1)
Length (cm)	
< 5	14 (50.0)
≥ 5	14 (50.0)
Median	8.8
Range	1-10.3

Chemotherapy

Chemotherapy consisted of cisplatin plus 5-fluorouracil or paclitaxel. Basically, cisplatin 26.67 mg/m^2/day was administered as 3-h infusion in N/S on days 1-3 for 2 courses 4 weeks apart, along with protracted infusion of 5-fluorouracil 500 mg/m^2/day, days 1-5 or paclitaxel 135 mg/m^2 given on day 1 as 3-h infusion in N/S or DW5. At 6 and 12 hrs before paclitaxel infusion, patients were administered 10 mg dexamethasone p.o and 300 mg i.v. cimetidine or 50 mg i.v. ranitidine, and 20 mg i.m. diphenhydramine. Chemotherapy was repeated after 28 days for a total of two courses.

Radiation therapy

Radiotherapy started concurrently with chemotherapy. Three-dimensional (3D) conformal radiotherapy was applied in this study. The positioning images of patients were obtained via CT simulator (General Electric, USA), and the range of scanning was from the mandibular angle to the lower edge of the third lumbar vertebra, with 5 mm thickness. The imaging data were transferred to the 3D radiotherapy planning system (Eclipse, Varian Medical Systems, Inc., USA) through network transmission. The gross tumor volume (GTV) was determined based on the results of CT, barium meal test, esophageal endoscopy and PET imaging. The clinical target volume (CTV) was determined based on GTV with 3-5 cm extension along the head and foot direction of the esophagus and 5 mm extension along the axial direction of the esophagus. In addition, the corresponding lymph node drainage area was determined based on different locations of the primary lesion, avoiding the anatomical barrier. The planning tumor volume (PTV) was formed by extending 8 mm in the head and foot direction and expanding 5mm in axial direction of CTV. Radiotherapy doses were 60Gy to GTV-P with 30 fractions in 6 weeks and 50Gy to CTV-P with 25 fractions in 5 weeks. Limitations of organs at risk were the maximum dose of the spinal cord less than 45Gy, the percent of lung volume V20 (irradiation volume greater than 20Gy) less than 30%, mean lung dose less than 16Gy, and cardiac V40 (irradiation volume greater than 40Gy) less than 35%. Linear accelerator (Clinac 23EX unit; Varian, Palo Alto, CA, USA) with 6MV high-energy rays for radiation treatment.

Table 2. Parameters of PET/CT and their meanings

Parameters	*Meanings*
MTV	Metabolic tumor volume greater than 40%SUVmax
SUVmaxpet1	SUVmax before radiotherapy and chemotherapy
SUVmaxpet2	SUVmax during radiotherapy of DT50Gy
SUVmaxpet3	SUVmax during radiotherapy of DT60Gy
SUVmaxpet4	SUVmax one month after radiotherapy
ΔS12	SUVmaxpet1-SUVmaxpet2
ΔS23	SUVmaxpet2-SUVmaxpet3
ΔS34	SUVmaxpet3-SUVmaxpet4
ΔS13	SUVmaxpet1-SUVmaxpet3
ΔS14	SUVmaxpet1-SUVmaxpet4
ΔR12	(SUVmaxpet1-SUVmaxpet2)/SUVmaxpet1
ΔR23	(SUVmaxpet2-SUVmaxpet3)/SUVmaxpet1
ΔR34	(SUVmaxpet3-SUVmaxpet4)/SUVmaxpet1
ΔR13	(SUVmaxpet1-SUVmaxpet3)/SUVmaxpet1
ΔR14	(SUVmaxpet1-SUVmaxpet4)/SUVmaxpet1

Follow-up

The follow-up assessment was carried out one month after the end of treatment and included esophageal barium meal test, chest CT and endoscopy of suspected recurrence. Subsequent assessments were carried out every 3 months for 6-40 months (median 18.5) with follow-up rate of 100%. Definitions of survival were as follows: PFS was defined as the time between treatment initiation and tumor progression or death from any cause; RFS was defined as the time between treatment initiation and tumor recurrence; OS referred to the time from the beginning of treatment to death from any cause. Disease progression was assessed by dynamic CT and barium meal examination and confirmed by gastroscopic biopsy or other means of biopsy, and was defined as enlargement of the primary tumor or metastatic lymph node, or appearance of new lesion(s).

Statistics

SPSS17.0 software was applied for statistical analyses. Nonparametric Mann-Whitney U test was used to compare differences in SUVmaxpet1, SUVmaxpet2, SUVmaxpet3, SUVmaxpet4, MTV before treatment, and the derived parameters. Kaplan-Meier method was used for survival analysis and log rank test was performed to assess differences in survival. Receiver operating characteristics curve (ROC) was used to obtain optimal threshold. Cox regression proportional hazard model was used to analyze the risk factors influencing survival time, with test level of $\alpha = 0.05$.

Results

Characteristics of enrolled patients

Of the 28 patients 18 were male and 10 female with median age of 58.5 years (range 46 – 80; Table 1). The anatomical disease localiza-

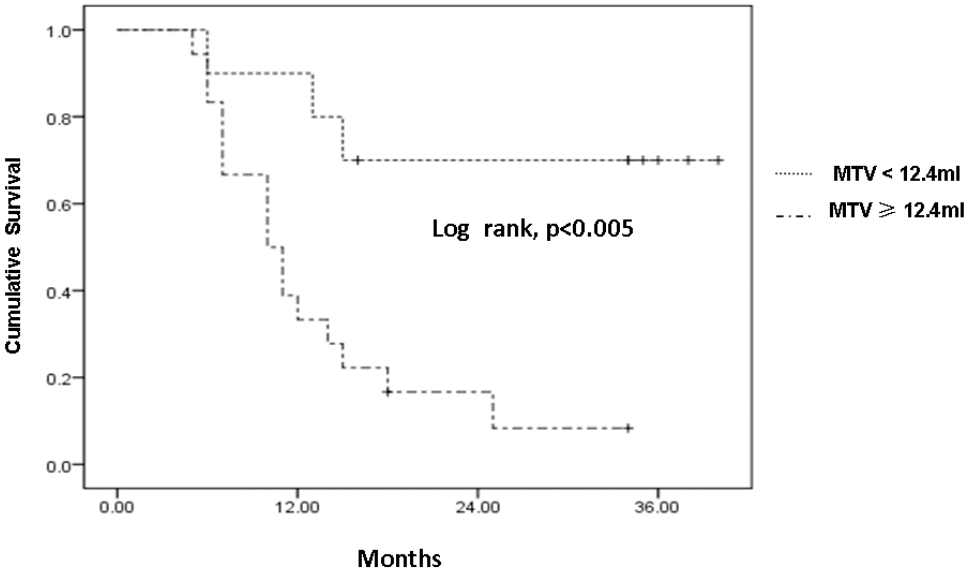

Figure 1. Overall survival analysis from the beginning of CCRT of esophageal cancer patients with different MTV values. Statistically significant difference in progression free survival in relation to metabolic tumor volume.

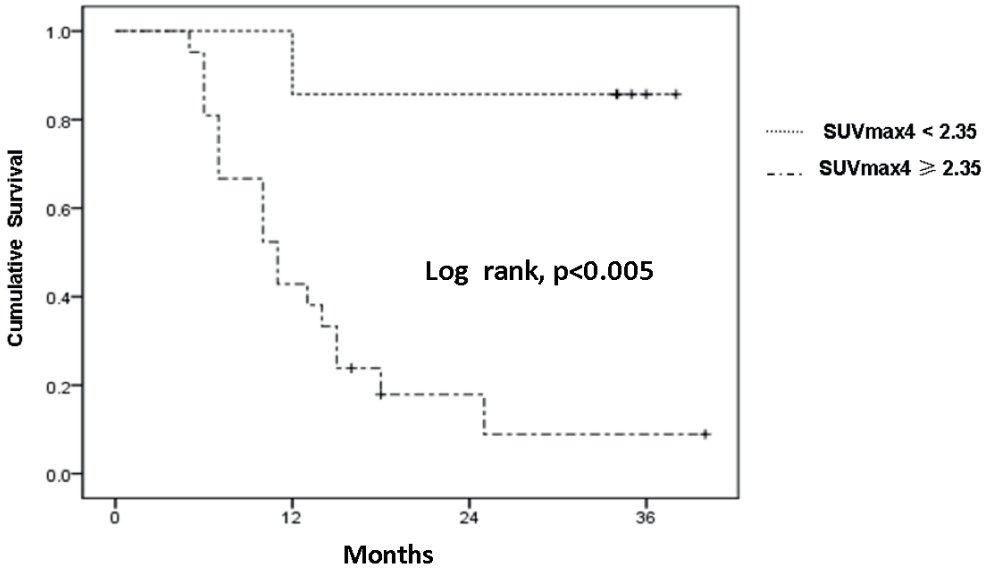

Figure 2. Overall survival analysis of esophageal cancer patients with different SUVmax4 values. Statistically significant difference in progression free survival in relation to SUVmax4.

tions are shown in Table 1. Pathological classification showed 2 cases of undifferentiated, 6 cases of poorly differentiated, 16 cases of moderately differentiated, and 4 cases of well-differentiated ESCC. Clinical stage distribution showed 6 cases of stage I, 8 of stage II, 11 of stage III and 3 of stage IV.

^{18}F-FDG PET/CT parameters

As shown in Table 3, the mean MTV value before treatment was 19.3 ml and the average SUVmax values at the 4 time points of scanning were 13.0 ± 7.4, 6.4 ± 3.2, 4.7 ± 1.9, and 3.4 ± 1.8, respectively. Mann-Whitney U test showed significant differences in MTV concerning PFS and RFS before treatment between positive and negative groups (p=0.003 and p=0.000, respectively). The results of nonparametric comparison showed that SUVmaxpet1 had no statistically significant difference in relation to PFS, RFS and OS, while the SUVmaxpet2 and SUVmaxpet3 showed significant difference concerning RFS. SUVmaxpet4 showed significant difference in relation to PFS, RFS and OS.

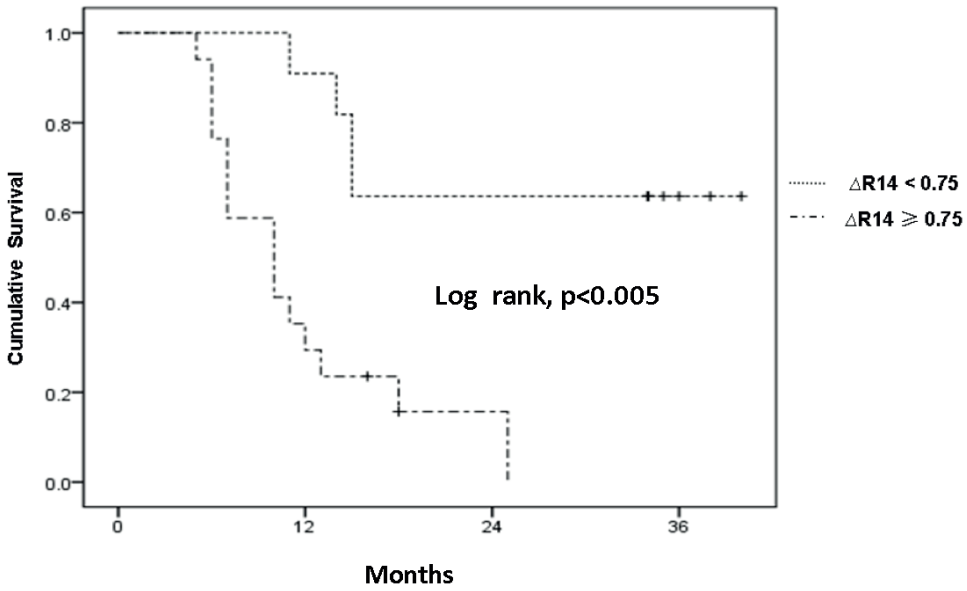

Figure 3. Overall survival analysis of esophageal cancer patients with different ΔR14 values. Statistically significant difference in progression free survival in relation to ΔR14.

Table 3. P values of differences of parameters in different survival groups (Mann-Whitney U test)

Parameters	*PFS*	*RFS*	*OS*
MTV	0.003	< 0.001	0.369
SUVmax-pet1	0.571	0.312	0.381
SUVmax-pet2	0.110	0.025	0.088
SUVmax-pet3	0.189	0.029	0.128
SUVmax-pet4	0.007	0.002	0.002
ΔS12	0.883	0.962	0.596
ΔS23	0.539	0.410	0.534
ΔS34	0.209	0.230	0.040
ΔS13	0.902	0.869	0.782
ΔS14	0.749	0.981	0.872
ΔR12	0.572	0.557	0.872
ΔR23	0.605	0.621	0.662
ΔR34	0.506	0.869	0.112
ΔR13	0.210	0.269	0.629
ΔR14	0.022	0.041	0.040
Site	0.627	0.959	0.960
Length	0.445	0.359	0.080
Age	0.786	0.869	0.764
Gender	0.139	0.396	0.067

PFS: progression free survival, RFS: relapse free survival, OS: overall survival

As shown in Table 4, Figure 1 and Figure 2, ROC curve was used to predict the optimal threshold (the maximum sensitivity and specificity) for RFS based on the values of MTV before the treatment. The result showed the optimal threshold was 12.4 ml, with the area under the curve (AUC) of 0.93, sensitivity of 0.94, and specificity of 0.82 ($p < 0.001$). Kaplan-Meier survival analysis showed the 3-year PFS and RFS in the group with MTV less than 12.4 ml were significantly higher compared with the group with MTV greater than 12.4 (3-year PFS 31.4 m vs 13.1 months, $p = 0.002$; 3-year RFS 36.6 vs 13.1 months, $p < 0.001$). The percents of 3-year PFS and RFS were 70 vs 11% and 90 vs 11%, respectively ($p<0.001$).

As shown in Table 5, multivariate Cox regression survival analysis revealed that MTV was an independent prognostic factor affecting PFS and RFS (risk ratio 1.13 and 1.14, respectively). Parameters of SUVmax, including the absolute value of SUVmax change and SUVmax change rate, were analysed with non-parametric Mann-Whitney U test. There was significant difference in ΔS23 in RFS. ΔS34 showed significant difference in RFS and OS, and ΔR14 showed significant difference in RFS and OS (Table 3). As analyzed by ROC curve, the optimal threshold of PFS and OS predicted by ΔR14 was 0.75. And the PFS, RFS and OS were relatively poor when reduction of ΔR14 was less than 0.75 (Figure 3). The statistical results of the remaining parameters are shown in Table 4. As shown in Table 5, the Cox multivariate regression analysis showed that MTV value greater than 12.4 ml was an independent factor for PFS and RFS ($p < 0.01$) before radiotherapy and chemotherapy.

Table 4. Kaplan-Meier single factor survival analysis of different survival groups

	PFS			*OS*			*RFS*		
	Threshold	*p-value*	*Median survival (months)*	*Threshold*	*p-value*	*Median survival (months)*	*Threshold*	*p-value*	*Median survival (months)*
MTV	12.4	0.002	31.4 vs 13.1	/	/	/	12.4	<0.001	36.6 vs 13.1
SUVmaxpet2	/	/	/	/	/	/	5	0.034	27.6 vs 14.6
SUVmaxpet3	/	/	/	/	/	/	4.5	0.001	29.3 vs 12.6
SUVmaxpet4	2.35	0.002	34 vs 14	3.7	0.001	34 vs 16.9	3.1	<0.001	34.2 vs 11.8
ΔR14	0.75	0.001	11.8 vs 30.4	0.75	0.003	17.2 vs 34.1	0.78	0.004	14.2 vs 33.4

Note: P values of SUVmaxpet1, ΔS12, ΔS23, ΔS34, ΔS13, ΔS14, ΔR12, ΔR23, ΔR34, ΔR13, parts of the body, length, age, gender were greater than 0.05. The optimal threshold was not calculated

Table 5. Cox multivariate analysis of factors impacting survival

Factors	*PFS*		*OS*		*RFS*	
	p-value	*Risk ratio*	*p-value*	*Risk ratio*	*p-value*	*Risk ratio*
Age	0.17	1.06	0.34	1.05	0.26	1.05
Length (CT)	0.31	1.15	0.06	1.31	0.12	1.27
T stage	0.11	2.35	0.28	1.9	0.78	1.23
MTV	< 0.001	1.13	0.51	1.03	< 0.001	1.14
SUVmaxpet2	0.63	0.96	0.47	1.10	0.66	0.96
SUVmaxpet3	0.43	0.87	0.99	1.00	0.61	0.91
SUVmaxpet4	0.76	0.94	0.46	0.85	0.56	1.16
ΔR14	0.08	0.07	0.14	0.09	0.47	0.28

Discussion

According to the results mentioned above, MTV value of ^{18}F-FDG PET/CT scanning before treatment was an independent factor for predicting prognosis of ESCC patients with non-surgical treatment. In addition, SUVmaxpet4 and ΔR14 measured one month after treatment could also predict prognosis of ESCC patients with non-surgical treatment. Four sequential ^{18}F-FDG PET/CT scannings were performed in our study and the indicators used were more objective and data were obtained by automatically measured software. Thus, our data from ^{18}F-FDG PET/CT scanning were less affected by factors such as window width and observers compared with the method of visual outline measurement.

Currently, SUVmax, as an observing indicator, is mainly used in ^{18}F-FDG PET/CT. However, it is still quite controversial to use the SUVmax value before treatment to evaluate the prognosis of esophageal cancer. Some researchers [8,9] claim that the survival could be predicted. However, the prediction accuracy for survival time of esophageal cancer using the SUVmax of the primary lesion before treatment was relatively poor [10-12]. In this study, it was found that SUVmax did not reflect the prognosis of patients before treatment. This could be probably attributed to the fact that SUV reflects only the level of glucose metabolism in tumor tissue, but not some other biological characteristics such as the sensitivity to treatment or tumor being prone to metastasis. Therefore, MTV was mainly used for prediction because it could reflect tumor information regarding the size of active tumor, tumor metabolism, and tumor burden.

In this study, the optimal threshold for predicting RFS was 12.4 ml. If this value was calculated in spherical lesions, the corresponding diameter was 2.87 cm, which was close to 3 cm and was normally considered as an easily controlled tumor diameter.

In the present study, univariate survival analysis indicated that SUVmaxpet2 and SUVmaxpet3 showed significant differences in RFS positive and negative groups. This may be because that after chemotherapy and radiotherapy, the relatively more sensitive cancer cells were killed and the residual cancer cells were insensitive or resistant to chemotherapy and radiotherapy, thus leading to higher accuracy in predicting RFS by SUV. Currently, radiotherapy and chemotherapy are the main treatment methods for non-surgical ESCC.

However, there is no recognized standard regarding the doses of radiotherapy and chemotherapy [13]. Therefore, for patients with relatively high SUVmaxpet2 and SUVmaxpet3 (as revealed by ^{18}F FDG PET/CT scanning), the curative effects may be improved through a further increase in radiation dose or the intensity of chemotherapy.

SUVmaxpet4 and ΔR14 all showed significant differences in both positive and negative groups of PFS, RFS and OS. Furthermore, their accuracies of prediction were all better than SUVmaxpet2, SUVmaxpet3 and MTV. This is probably because the local inflammation had subsided, and the residual tumor cells resistant to therapy had recovered and even proliferated. Therefore, ^{18}F FDG PET/CT could reflect the number of residual tumor cells and thus predict survival more accurately [14].

It was found that ΔS23 showed significant differences in RFS positive and negative groups. This may be caused by the inhibited proliferation of tumor cells in the late stage. The greater ΔS23 value indicates poorer ability of tumor cell proliferation in the late stage thus producing better prognosis. However, significant differences were not found in univariate survival analysis. This may indicate that not all the patients with ESCC have late-stage accelerated proliferation of tumor cells. ΔS34 showed significant differences in both RFS, OS positive and negative groups, suggesting that the prognosis was better if the metabolic activity of the tumor was further decreased at the end of treatment. An explanation could be that the cells have lost the capacity of continuous passage even if there are still residual tumor cells after radiotherapy and chemotherapy.

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