

Original Article

¹⁸F-FDG PET-CT metabolic findings can predict the short-term curative effects in esophageal cancer

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Abstract: Objective: ¹⁸F-FDG PET-CT is a noninvasive approach extensively used to assess the therapeutic results and give a prognosis for esophageal cancer. This study is focused on examining the predictive value of metabolic tumor volume (MTV) and pre-treatment maximal standardized uptake value (SUVmax) of short-term curative effects demonstrated in patients with esophageal cancer. Methods: This study carried out a retrospective analysis of 98 patients diagnosed with esophageal cancer who received treatment by radiotherapy or a combination of chemotherapy and radiotherapy in the Second Affiliated Hospital of Fujian Medical University. ¹⁸F-FDG PET-CT scan was carried out prior to the treatment. PET/CT images before treatment were evaluated by two high-level professional doctors as a double-blind method. MTV and SUVmax values were averaged and confirmed. In 1 to 3 months after the treatment, a deputy director of PET/CT center with much experience and a radiotherapist assessed the curative effect of all patients in line with the Response Evaluation Criteria in Solid Tumor (RECIST). Results: No considerable difference in SUVmax and MTV was observed between the two groups in cancer site, gender, age, or differential extent. In addition, there was a significant correlation between SUVmax and lesion length, lymph node metastasis, depth of invasion, and clinical stage. SUVmax was positively correlated to depth of invasion, lymph node metastasis, MTV, lesion length, and clinical stage. The value of effective rate was up to 67.3% (66/98). There was a negative correlation between MTV as well as SUVmax, and curative effects in the short term, whereas the curative effects of MTV exceeded that of SUVmax. Conclusion: MTV and SUVmax before treatment serve to forecast curative effects in the short term of radiotherapy or combination of chemotherapy and radiotherapy for patients with esophageal cancer. MTV had a greater predictive effect than SUVmax.

Keywords: PET-CT, esophageal tumor, maximum standard uptake value, tumor metabolic volume, curative effect

Introduction

Esophageal cancer is the third most common gastrointestinal malignancy in the world [1]. In China, squamous cell carcinoma is the most common type of esophageal cancer and is also highly sensitive to radiation. Due to lower trauma and better survival, radiotherapy plus chemotherapy has become a widely accepted local esophageal cancer treatment mode [2]. Treatment techniques continue to improve, but the prognosis of esophageal cancer is still poor. In clinical practice, prior to radiotherapy and chemotherapy, the application of noninvasive methods for more accurate prediction of the curative effect is of great significance. It can improve the curative effect of cancer patients, develop reasonable individual treatment programs,

reduce the suffering of patients from improper examination, and reduce the economic burden. Especially, most patients with esophageal squamous cell carcinoma at the time of seeing a doctor are at advanced stage [3]. Due to long-term poor and unbalanced nutrition, most patients get weight loss, anemia, water and electrolyte disorders, hypoproteinemia, and inability to tolerate repeated invasive inspections and cannot adjust to the treatment program in case of poor curative effect [4].

As a new type of auxiliary examination, ¹⁸F-FDG PET-CT can detect a lesion prior to organ anatomy through the high metabolic function of tumor cells in fluorodeoxyglucose (FDG). In malignant tumors, it is mainly used to indicate glucose metabolism of the entire tumor tissue

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[5]. At present, ^{18}F -FDGPET-CT is widely used to assess post-treatment effect and prognosis in the various stages of tumor and guide the precise positioning of a radiotherapy target [3-7]. The maximal standardized uptake value (SUVmax) of primary tumor in FDG is the ^{18}F FDG uptake index reflected by ^{18}F -FDG PET-CT, which is often used to predict the prognosis or evaluate the curative effect of patients with tumor [8]. The uptake value (SUV) of primary tumor in FDG is the most commonly used semi-quantitative parameter index of FDG PET scanning, which can more accurately reflect the active degree of glucose metabolism in tumor tissue; and SUVmax in the region of interest has become the most commonly used indicator of prognosis in clinics because of its better stability and reproducibility [9-12]. MTV of primary tumor is a quantitative measure that reflects the number of tumor cells with abnormal glucose metabolic activity. It can demonstrate the combination of tumor volume and functional metabolism, and its size reflects the level of tumor load. These two indicators as a reliable prognostic factor have been widely used in a variety of solid tumors, such as lung cancer, pleural mesothelioma, ovarian cancer, and head and neck cancer [3, 13-15].

However, the predictive value of SUVmax and MTV on short-term curative effect of non-surgical esophageal squamous cell carcinoma (ESCC) before treatment has not yet been reported. Retrospective analysis is made in this study for 98 cases of esophageal cancer patients receiving radiotherapy or radiotherapy combined with chemotherapy from January 10th, 2016 to January 26th, 2018 in the Second Affiliated Hospital of Fujian Medical University, in order to explore the predictive value of pre-treatment SUVmax and MTV on the short-term curative effect in esophageal cancer patients treated with radiotherapy or radiotherapy combined with radiotherapy.

Material and methods

General information

Esophageal cancer patients receiving radiotherapy or radiotherapy combined with chemotherapy from January 10th, 2016 to January 26th, 2018 in Second Affiliated Hospital of Fujian Medical University were selected. Inclusion criteria: (1) patients receiving initial treat-

ment who could not be subject to or refuse surgery; (2) pathologic type: squamous cell carcinoma confirmed by cytology or histopathology; (3) complete inspections performed before treatment (illness history collection, physical exam, laboratory exam, PET-CT, esophageal barium meal exam, chest CT, abdominal ultrasound exam, electrocardiogram); post-treatment esophageal barium meal exam, chest CT exam or esophageal microscopy data; (4) no other primary tumor exists concurrently; (5) consistency with intensity modulated radiation therapy requirements. Exclusion criteria: Locally advanced patients who could not receive surgery; advanced patients who received palliative radiotherapy; patients at early and mid-stages who received preoperative adjuvant treatment; patients at early stage who refused surgery but underwent radical treatment. These patients underwent ^{18}F -FDG PET-CT. Moreover, these patients were divided into groups in which were compared with regard to SUVmax and MTV.

Radiotherapy

All patients received intensity modulated conformal radiotherapy, 95% PTV dose was 60-64 Gy in single radiotherapy, and 56-60 Gy in combination with chemotherapy. For the normal tissue and organs, the dose controlled in the lungs (V20) was $\leq 30\%$, maximum dose in spinal cord ≤ 45 Gy, heart V30 $\leq 33\%$ and V50 $\leq 67\%$, liver V35 $\leq 50\%$. Cisplatin (PDD) for injection was from QILU Pharmaceutical Ltd (Approval No. H37021358), 5-Fluorouracil for Injection from Shanghai Xudong Haipu Pharmaceutical Ltd (Approval No. H31020593), and Calcium Folate (CF) for Injection from Wuhan Li Shizhen Pharmaceutical Ltd of Huangshi Li Shizhen Pharmaceutical Group (Approval No. H20045709).

Chemotherapy

66 patients have received chemotherapy previously. The chemotherapy regimen was DDP-5-FU or DDP-CF/5-FU. DDP-5-FU regimen: Intravenous drip of PDD at 20 mg/m² for 1 h on days 1-5 + continuous pumping of 5-Fluorouracil (5-FU) at 750-1000 mg/m² for 24 h on days 1-5; 21 days constituting 1 course. DDP-CF/5-FU regimen: Intravenous drip of PDD at 20 mg/m² for 1 h on days 1-5 + intravenous drip of CF at 100 mg/m² for 2 h on days 1-5 + intravenous

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drip of 5-FU at 350-400 mg/m² for 2-3 h on days 1-5; 21 days constituting a course. There are 1-4 chemotherapy courses.

PET-CT scan

The Gemini TF 64 PET/CT instrument (Philips, the Netherlands) was used. ¹⁸F-FDG was generated from Sumitomo Corporation HM-10 cyclotron, with the radiochemical purity greater than 95%. Before the examination, patients fasted for more than 6 hours, and blood glucose levels were controlled below 6.1 mmol/L. After intravenous injection of 0.10-0.15 mCi/kg ¹⁸F-FDG, patients had a rest for 60 minutes. After urination, the patients were scanned on the machine in a supine position. CT-scan acquisition parameters were 120 kV, 200 mA, matrix 512 * 512, layer thickness 5 mm. PET images were acquired from cricothyroid membrane to the superior mesenteric artery. The acquisition of images was performed by a three-dimensional model, then attenuation correction was made by CT data. The fusion of PET and CT images was performed on EBW2.0 post-processing workstation, to get the PET, CT and PET/CT fusion images of cross-section, sagittal, and coronal plane. The maximum standard uptake (SUVmax) was measured by ROI (region of interest, ROI).

Short-term curative effect evaluation criteria

1-3 months after treatment, the patients underwent lab exam, esophageal barium meal exam, abdominal ultrasound, chest CT or ¹⁸F-FDG PET/CT scan. An experienced deputy director of PET/CT center and a radiotherapist evaluated the curative effect of all patients according to the Response Evaluation Criteria in Solid Tumor (RECIST). Short-term effects are below: complete remission (CR), partial remission (PR), stable disease (SD) and progressive progression (PD). In this study, the treatment would be considered effective if the treated patient was with CR or PR, and ineffective if the treated patient had SD or PD.

SUVmax and MTV calculation

Visual inspection and semi-quantitative analysis were used for the SUVmax and MTV calculation. Visual inspection was performed to know the uptake degree of ¹⁸F-FDG by the lesion, in order to determine the threshold of optimal

SUV as region of interest (ROI) in automatic delineation. SUVmax of primary tumor was measured by ROI. The imaging area is the metabolic active region with its boundary delineated slice by slice. The area of each slice is multiplied by slice thickness to obtain the volume of each slice. The accumulation method was used to calculate MTV in ESCC patients. If SUVmax was < 2.5, then MTV would be calculated according to 0.1 cm³. In the determination of MTV, the high metabolic area in PET images was excluded. PETV CT images before treatment were read two PET-CT physicians with a high title with SUVmax and MTV being determined and averaged.

Statistical analysis

SPSS13.0 statistical software was used in analysis. The mean value of the measured data was expressed as $\bar{x} \pm s$. The correlation of SUVmax and MTV with lesion length was analyzed by Pearson correlation method. Spearman correlation method was used to analyse the correction of SUVmax and MTV with depth of invasion, differentiation extent, lymph node metastasis and short-term efficacy. T-test or ANOVA was used to compare clinical factors with SUVmax and MTV of short-term effect. $P < 0.05$ was considered significant.

Results

Impact of clinical factors on SUVmax and MTV of primary tumor

There were 98 patients included in this study (**Tables 1** and **2**). There was no significant difference of SUVmax and MTV between two groups in age, sex, esophageal cancer site, or differentiation extent ($P > 0.05$). There was a significant difference of SUVmax and MTV between two groups in lesion length, depth of invasion, lymph node metastasis, and clinical stage ($P < 0.05$). Further correlation studies indicated that SUVmax and MTV were positively correlated with lesion length, differentiation, depth of invasion, and clinical stage ($P < 0.05$).

Correlation of SUVmax and MTV with short-term curative effect after radiotherapy and chemotherapy

At treatment, 40 patients (40.8%) achieved CR, 26 (26.5%) PR, 27 (27.6%) SD, and 4 (4.1%) PD. The total effective rate (CR + PR) was 67.3% (66/98). SUVmax values of effective and inef-

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Table 1. Impact of clinical factors on SUVmax

Factor	n	SUVmax	Statistics	P value
Age			t = 0.5611	0.5774
< 63.9	40	12.22 ± 5.465		
> 63.9	58	11.39 ± 4.489		
Gender			t = 1.616	0.1127
Male	78	11.3 ± 4.828		
Female	20	14.15 ± 5.55		
Site			F = 0.3743	0.7720
Neck	7	11.4 ± 5.84		
Upper thoracic	22	12.55 ± 5.306		
Middle thoracic	50	12.18 ± 5.388		
Lower thoracic	19	10 ± 1.717		
Lesion length			t = 2.261	0.0284
< 6.9	42	10.07 ± 4.981		
> 6.9	56	13.24 ± 4.757		
Differential extent			F = 1.110	0.3384
Low	38	11 ± 5.168		
Medium	44	11.81 ± 4.729		
High	16	14.16 ± 5.615		
Invasion depth			F = 4.201	0.0211
T2	10	7.2 ± 4.096		
T3	52	11.06 ± 4.6		
T4	36	13.99 ± 5.047		
Lymph node metastasis			t = 2.203	0.0326
No	10	7.34 ± 3.736		
Yes	88	12.4 ± 4.957		
Clinical stage			F = 2.893	0.0305
II	12	10.13 ± 8.355		
IIIA	30	10.85 ± 4.154		
IIIB	18	12.07 ± 4.575		
IIIC	20	13.14 ± 3.647		
IV	18	14.37 ± 4.607		

fective groups were 14.84 ± 8.468 and 21.13 ± 12.8 , $t = 2.052$, $P = 0.045$, respectively. MTV values were 10.38 ± 4.053 and 14.98 ± 5.62 , $t = 3.277$ and $P = 0.002$, respectively. Further correlation studies showed that SUVmax and MTV were negatively correlated with short-term effect. The correlation coefficients were -0.283 ($P = 0.049$), -0.379 ($P = 0.007$), respectively, and correlation of MTV was stronger than that of SUVmax (Table 3).

Discussion

A large number of studies has shown that SUVmax and MTV are correlated with esophageal cancer invasion ability, distant metastasis

risk, tumor response and prognosis of patients, but the correlation of SUVmax and MTV with gender, age, lesion length, depth of invasion, metastatic status, and other clinical factors is still unclear [16-18]. Huang et al. [12] found in observing relationships of patient age and gender, that with SUVmax and MTV of 40-50 year-old patients were higher than that of 80-90 year-old patients, but there was no significant difference of SUVmax and MTV between males and females. In this study, we compared the SUVmax and MTV of esophageal cancer patients with different age and gender, respectively, and found that there was no significant difference in SUVmax and MTV between different age groups and between males and females. The impact of age on SUVmax and MTV of esophageal cancer patients still needs clinical data for further analysis. Park et al. [19] retrospectively analyzed the relationship of SUVmax and MTV with lymph node metastasis in 25 cases of esophageal cancer, and found that their positive correlation existed. Yamada et al. [20] retrospectively analyzed the relationship between PET/CT and lymph node metastasis in 258 patients with esophageal cancer, with the results showing that lymph node metastasis was correlated with SUVmax and MTV, but the correlation was limited by the size of metastatic lymph

nodes. Park et al. [21] compared the relationship between PET/CT and lesion infiltration and lymph node metastasis in patients with neoadjuvant and non-neoadjuvant therapy. It was found that in patients receiving non-neoadjuvant therapy, lesion infiltration and lymph node metastasis were associated with SUVmax and MTV; in patients receiving new adjuvant therapy, lesion infiltration was associated with SUVmax and MTV, but lymph node metastasis was not. Current study found that SUVmax and MTV were positively correlated with lesion length, depth of invasion, lymph node metastasis, and clinical stage, which is consistent with results of the above study.

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Table 2. Impact of clinical factors on MTV

Factors	n	MTV	Statistics	P
Age			t = 0.2073	0.8367
< 63.9	40	17.27 ± 9.544		
> 63.9	58	16.63 ± 11.09		
Gender			t = 1.886	0.0655
Male	78	15.51 ± 9.243		
Female	20	22.28 ± 13.19		
Site			F = 0.3989	0.7544
Neck	7	16.12 ± 13.41		
Upper thoracic	22	19.96 ± 13.58		
Middle thoracic	50	16.06 ± 8.57		
Lower thoracic	19	15.66 ± 8.456		
Lesion length			t = 2.342	0.0235
< 6.9	42	12.69 ± 10.17		
> 6.9	56	19.22 ± 9.284		
Differential extent			F = 1.660	0.2014
Low	38	15.95 ± 9.346		
Medium	44	15.52 ± 9.357		
High	16	22.91 ± 14.23		
Invasion depth			F = 5.579	0.0068
T2	10	6.985 ± 4.723		
T3	52	14.69 ± 9		
T4	36	21.98 ± 10.74		
Lymph node metastasis			t = 2.386	0.0211
No	10	6.51 ± 3.279		
Yes	88	17.8 ± 10.43		
Clinical stage			F = 2.893	0.0305
II	12	7.975 ± 6.448		
IIIA	30	14.69 ± 9.668		
IIIB	18	19.25 ± 9.174		
IIIC	20	21.27 ± 6.478		
IV	18	21.54 ± 12.677		

Table 3. Correlation of SUVmax and MTV with lesion length, depth of invasion, and lymph node metastasis

Correlation analysis	Correlation coefficient	P
SUVmax and lesion length	0.473	0.001
SUVmax and depth of invasion	0.391	0.005
SUVmax and lymph node metastasis	0.304	0.034
SUVmax and clinical stage	0.290	0.043
SUVmax and short-term curative effect	-0.283	0.049
MTV and lesion length	0.376	0.008
MTV and depth of invasion	0.462	0.001
MTV and lymph node metastasis	0.356	0.012
MTV and clinical stage	0.419	0.003
MTV and short-term curative effect	-0.379	0.007

At present, there is no consensus on ability of FDG-PET/CT metabolic parameters to predict the efficacy of radiotherapy and chemotherapy. MTV is reported to be a better survival predictor in lung cancer, ovarian cancer, head and neck cancer, and pleural mesothelioma. Miyata et al. [22] retrospectively analyzed the pre-treatment SUVmax as a prognosis indicator in 211 patients with esophageal cancer, with results showing that it was correlated with recent curative effect, local control, progression-free survival, and long-term survival in radiotherapy and chemotherapy of esophageal cancer. Li et al. [23] adopted SUVmax, MTV, and PET primary tumor length to study the prognosis value of PET in patients with esophageal cancer, and found that SUVmax, MTV, and PET primary tumor length could predict the overall survival rate. However, Chang et al. [24] adopted MTV, SUVmax, SUVmean, PET primary tumor length and TNM to evaluate the prognosis, and found that MTV was the only indicator related with prognosis. Our findings suggest that SUVmax and MTV can predict the short-term effect of radiotherapy or radiotherapy in patients with esophageal cancer, but MTV is more predictive than SUVmax. The inconsistency of above findings may be due to differences in inclusion criteria, pathologic type, and effect evaluation criteria.

There are still a number of deficiencies in the current study. Only 98 cases were included, which may lead to potential selection bias and may result in significant differences in survival or prognosis due to differences in staging and differentiation; and its correlation with SUVmax and MTV was analyzed separately from lesion length, depth of tumor invasion, lymph node metastasis, and clinical staging. Whether there are independent factors between them needs to be verified in the further study. Moreover, the results from only the

choice of objective response rate as a short-term effect indicator are not sufficiently objective and comprehensive.

Disclosure of conflict of interest

None.

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