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

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Abstract. *Aim: To investigate the prognostic role of the pretreatment metabolic tumor volume (MTV) as determined by Positron emission tomography - computed tomography (PET-CT) in patients with esophageal cancer undergoing curative surgery. Patients and Methods: We retrospectively reviewed the data of 26 patients with squamous cell carcinoma of the esophagus, who underwent ^{18}F-Fluorodeoxyglucose PET-CT before surgery. MTVs were defined as the volumes with FDG uptake above a standardized uptake value (SUV) of 2.5 (MTV2.5), or a fixed threshold of 20% (MTV20%) of the maximum intratumoral activity. Overall survival (OS) and disease-free survival (DFS) were examined by the Kaplan-Meier method and the log-rank test. Results: In a median follow-up of 15 months, 13 patients had died. The mean MTV2.5 was 18.9±15.4 ml (median, 16.0), whereas the mean MTV20% was 21.7±15.0 ml (median, 19.1). Patients who had tumors of an MTV2.5 >16.0 ml had an inferior one-year OS compared with patients with a lower MTV2.5 (70% vs. 84%, p=0.018). Similarly, patients with an MTV20% >19.1 ml had poorer outcomes compared with patients who had small tumors, with one-year OS of 69% and 85%, respectively (p=0.016). No statistical significance was found in DFS for both MTV approaches. The $SUV_{p\text{-}max}$ had no impact on the OS and the DFS when using a median value of 8.3. Conclusion: Pretreatment MTV is a novel marker for OS of patients with esophageal cancer treated with curative surgery. For those with higher MTVs, more aggressive adjuvant treatments should be considered.*

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Esophageal cancer (EC) is a disease of dismal outcome, and most tumors are locally-advanced at initial diagnosis (1). Currently, radical esophagectomy with or without upfront chemoradiotherapy (CRT) is the mainstay of treatment for early-stage disease; however, the outcome is not satisfactory because most of the patients still experience locoregional recurrence or distant metastasis (2, 3).

The traditional TNM classification has been widely used as a prognostic factor in patients with cancer (4, 5), and the current American Joint Committee on Cancer (AJCC) staging system for EC is controversial because it attributes too much importance to the depth of invasion and emphasizes on the involvement of lymph nodes (6).

A part from computed tomography (CT) or magnetic resonance imaging (MRI), which are predominantly based on morphological changes, functional imaging techniques, such as ^{18}F-fluorodeoxyglucose positron-emission (^{18}F-FDG-PET), are widely used as imaging tools in staging and predicting therapy response for various types of cancer, including EC (7, 8). Although the prognostic value of FDG-PET-related parameters in EC remains controversial (9), PET computed tomography (PET/CT) is an increasingly popular imaging modality. In particular, a PET/CT scan incorporates both anatomic localization and functional information, which improve the accuracy of staging. Theoretically, a high

standardized uptake value (SUV) for tumors might imply a higher chance of tumor aggressiveness. Nonetheless, a review of research has not conclusively proven the predictive value of the maximum SUV (SUV_{max}) across 15 studies in patients with EC following surgery (9). In addition, only two studies have proved the independent role of SUV_{max} on survival (10). These discrepancies might be attributed to the heterogeneity of treatment modalities, the use of several endpoints, and the use of various SUV_{max} cut-off points.

On the other hand, metabolic tumor volume (MTV), defined as the volume of tumor tissues with increased glycolytic activity, is a novel index which combines the information of SUV uptake and tumor volume. Three studies on head and neck cancer have suggested that MTV may predict radiotherapy or CRT outcome (11, 13). However, one study has explored the impact of pretreatment MTV on survival in EC patients (14) and they concluded that MTV, as a volumetric parameter of ^{18}F-FDG PET, is an important independent prognostic factor for survival in addition to TNM staging. In addition, an optimal approach in determining the MTV remains unsolved. Possibly, studies using homogeneous pathological type and treatment modalities would be able to establish a role for the best application of the MTV for future treatment individualization.

This study was conducted to test the hypothesis that pretreatment MTV can predict the survival of patients with EC undergoing curative surgery. Two MTV methods were examined. To minimize the effect of treatment modalities on outcome, we only included squamous cell carcinoma of the esophagus, treated with curative esophagectomy. Our results may help oncologists assess an aggressive adjuvant therapy for patients at high risk, or select a suitable case selection for surgery.

Patients and Methods

Patient population. We retrospectively reviewed the medical records of 26 patients with squamous cell carcinoma of the esophagus diagnosed at the China Medical University Hospital between October 2009 and April 2010 (Table I). All patients underwent preoperative PET/CT within 8 weeks before the planned esophagectomy. This study was approved by the Ethical Committee of the hospital (DMR-99-IRB-010-2).

PET-CT imaging protocol. All patients were asked to fast for at least four hours prior to FDG-PET-CT scanning. A PET-CT scanner (Discovery STE; GE Medical Systems, Milwaukee, WI, USA) was used to obtain the image. Whole-body FDG-PET-CT images were acquired approximately 45 min after intravenous injection of 370 MBq (10 mCi) of FDG. PET emission images were obtained after CT scans at 2 min per field of view (FOV) in the 3-dimensional acquisition modes. These CT images were reconstructed onto a 512×512 matrix with a section thickness of 3.75 mm, reconstructed onto a 128×128 matrix, and converted into 511-keV-equivalent attenuation factors for attenuation correction of the corresponding PET emission images. The SUV_{max} of EC and metastases on delayed FDG-PET-CT images were obtained. This procedure has been described in our previous report (15).

MTV definition and measurement. MTVs were measured from attenuation-corrected FDG-PET images using an SUV-based automated contouring program (Advantage Workstation Volume Share version 2; GE Health, Milwaukee, WI, USA). FDG-PET data in DICOM format were introduced into the workstation and these images were reviewed in order to localize the target lesions, which had been confirmed by two nuclear medicine physicians. MTV was defined as the sum of metabolic volumes of the primary tumors where the volume boundaries were drawn sufficiently wide to incorporate each target lesion in the axial, coronal, and sagittal FDG-PET images. In this study, two methods for the MTV were used. MTV2.5 was the volume with FDG uptake above an SUV value of 2.5, while MTV20% was determined as the volume more than a fixed threshold of 20% of the maximum intratumoral activity. The reason we selected the two methods was that the optimal threshold could be defined when the maximum metabolic tumor length was exactly the same as the pathological tumor length, as described in our previous study (16). The MTVs for the primary site were allowed to include adjacent lymph nodes with small volumes. When small lymph nodes adjacent to the primary tumor look like part of the primary lesion, they cannot be distinguished from the primary tumor by PET/CT. However, large lymph nodes neighboring to the primary tumor can be determined by automatic volumes of interest tool on PET/CT, even if they are partially contiguous with the primary tumor. Figure 1 shows the contours of the MTVs in a patient with T3N0M0 squamous cell carcinoma of the esophagus. The SUV_{max} for the primary tumor was also recorded and abbreviated as $SUV_{p\text{-}max}$.

Although visual interpretation can be used to evaluate MTV, our study did not include this method because it is susceptible to variations caused by window level settings, and is highly operator-dependent. These influences may lead to wide variability among institutions.

Treatment and follow-up. The details of surgical procedure were described previously (15). After surgery, all patients were followed-up every one to two months over the first two years, and every three to four months thereafter. A CT scan of the chest was performed every four to six months over the two years, whereas PET/CT was performed when local recurrence or distant metastasis was suspected. The definition of recurrence (locoregional relapse or distant metastasis) was based on the CT scan of the chest or PET/CT, or both. The follow-up period for all patients ranged from 3 to 28 months (median=15 months).

Statistical analysis. Patients were divided into two groups according to the median values for the MTV2.5 and the MTV20%. Correlations between MTV and SUV_{max} were examined using the Pearson's correlation, with the alpha level set at 0.01. The study endpoints were overall survival (OS) and disease-free survival (DFS). 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 statistical tests were two-sided and performed at the 5% level of significance by using the SPSS Software for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA) and *p*-values of less than 0.05 were considered statistically significant.

Table I. *Patients' characteristics.*

Characteristic	No of patient
Age, years	
Median	42-72
Range	60.4
Gender	
Male	26
Female	0
Tumor location	
Upper 1/3	12
Middle 1/3	11
Lower 1/3	3
AJCC stage (pathology)	
I	4
II	9
III	7
IV	6
Cause of failure	
Local recurrence	1
Distant metastasis	7
Local recurrence & distant metastasis	4
Other	1
Overall Survival	
Alive	13 (50%)
Dead	13 (50%)

Results

Treatment outcome. After a median follow-up duration of 15 months (range 3 to 27 months), 13 patients died. One died of another disease, one died of local recurrence and four died due to both local recurrence and distant metastasis; seven patients died because of distant metastasis. Twelve patients (46.1%) developed recurrences at the primary site, with or without nodal failure. In all, the one-year OS and DFS were 75% and 84%, respectively.

Prognostic value of MTV. The mean $SUV_{p\text{-}max}$ was 7.4±3.8 (median=8.3; range=2.4 to 14.9). The two methods for calculating MTV values were used successfully for all patients. The mean MTV2.5 was 18.9±15.4 ml (median=16.0 ml; range=1.1 to 51.5 ml), whereas the mean MTV20% was 21.7±15.0 (median=19.1 ml; range=4.4 to 59.7 ml). Our data revealed some correlation between the MTV2.5 and the SUV_{max} (r=0.58, p=0.002), but reduced correlation between the MTV20% and the SUV_{max} (r=0.45, p=0.02). The distributions of $SUV_{p\text{-}max}$, MTV2.5 and MTV20% with respect to T classification are shown in Table II.

The effects of the $SUV_{p\text{-}max}$ and MTVs on OS and DFS were analyzed by univariate analysis. As shown in Figure 2, patients who had tumors of an MTV2.5 >16.0 ml had an inferior one-year OS compared with patients with a lower MTV2.5 (70% *vs*. 84%, p=0.018). Similarly, patients with a MTV20% >19.1 ml had poorer outcomes compared with patients who had small tumors, with a one-year OS of 69% and 85% (p=0.016), respectively (Figure 3). No statistical significance was found in the DFS for both MTV approaches. The $SUV_{p\text{-}max}$ had no impact on the OS or the DFS when using the median value of 8.3.

Table II. *The distribution of the Standardized uptake value maximum for the primary tumor ($SUV_{p\text{-}max}$) and metabolic tumor volumes (MTVs) with respect to T classification.*

Patient	Tumor location	Pathology tumor staging (pT)	$SUV_{p\text{-}max}$	
			MTV2.5	MTV20%
1	M/3	2	2.7	4.4
2	M/3	2	1.5	8.0
3	U/3	3	21.7	24.3
4	L/3	3	38.2	41.8
5	U/3	3	23.6	32.2
6	U/3	3	15.6	18.0
7	U/3	4	19.0	20.2
8	M/3	3	10.2	19.1
9	U/3	1	1.1	6.3
10	M/3	4	51.5	59.7
11	U/3	3	43.0	46.2
12	U/3	3	42.7	39.5
13	M/3	2	19.2	19.0
14	U/3	3	31.4	33.0
15	U/3	3	2.8	4.4
16	U/3	4	21.2	20.7
17	M/3	1	0.0	4.4
18	M/3	1	3.7	4.4
19	L/3	3	38.0	34.0
20	M/3	3	25.6	26.3
21	M/3	1	11.1	19.0
22	M/3	3	5.2	7.6
23	M/3	3	16.0	19.2
24	U/3	4	0.00	4.4
25	L/3	3	35.5	35.5
26	U/3	3	11.3	12.1

L/3: Lower one-third; M/3: middle one-third; U/3: upper one-third.

Discussion

Identification of factors predictive of treatment outcome in cancer patients is always of great potential interest, since such research may allow for therapy to be tailored to the exact characteristics of individual tumors. With the variations in tumors nature treatment results might be optimized if prognostic factors, such as information from molecular imaging or others biomarkers, could be used to supplement the clinical stage. This preliminary study used PET-related parameters, such as SUV_{max}, and two MTV estimation methods, to investigate the postoperative outcome in patients with early-stage EC. We attempted to limit heterogeneity by

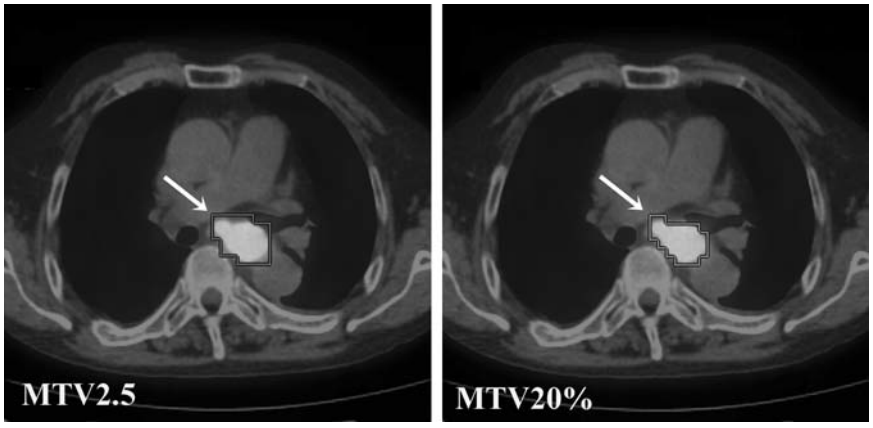

Figure 1. *Metabolic volumes of the primary tumors of a T3 squamous cell carcinoma patient (arrow). The Positron emission tomography area was delineated by an isocontour with a Standardized uptake value maximum of 2.5 (MTV2.5) (a) and 20% of SUV_{max} (MTV20%) (b).*

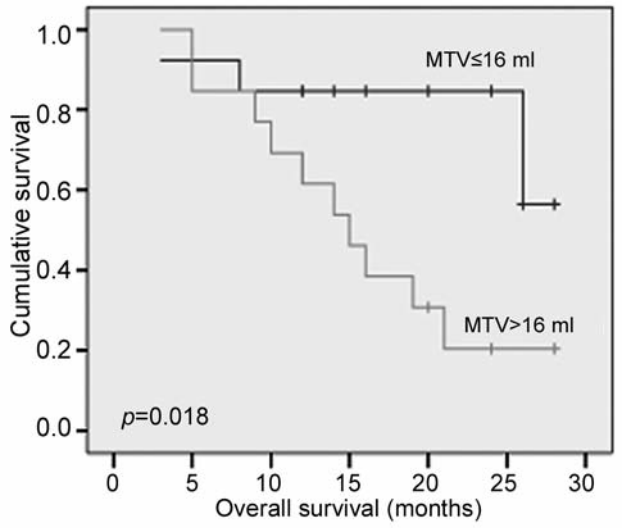

Figure 2. *Overall survival according to the median MTV2.5 (MTV2.5 >16 ml vs. ≤16 ml (p=0.018).*

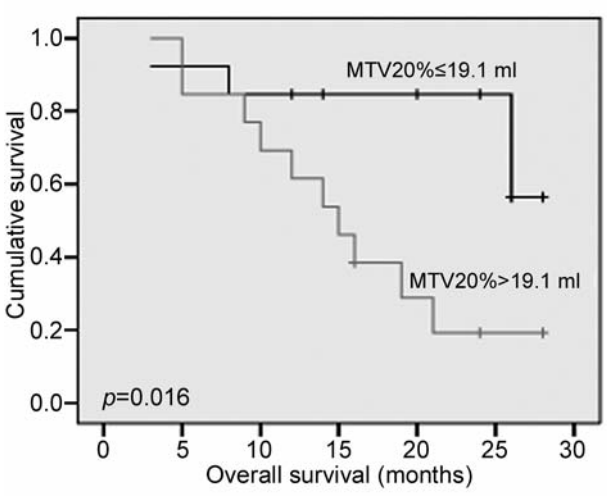

Figure 3. *Overall survival according to the median MTV20% (MTV2.5 >19.1 ml vs. ≤19.1 ml (p=0.016).*

restricting our analysis to patients with a histological type of squamous cell carcinoma without neoadjuvant CRT. The two MTVs tested showed concurrently a trend of novel markers for OS in patients undergoing curative surgery. Our findings were consistent with the hypothesis that a large tumor burden together with fixed FDG uptake might represent a relatively aggressive tumor, as evidenced by proliferative activity, hypoxia, low apoptosis rate, and p53 overexpression, as described in some molecular studies (17-19).

Traditionally, CT or MRI in combination with information from endoscopic ultrasound is used to provide the anatomic information in EC. However, the greatest tumor diameter cannot represent the real tumor size or tumor burden because a tumor does not always have a uniform shape. In addition, it might be difficult to determine the boundary of the primary tumor of the esophagus by simply using contrast-enhanced chest CT (20, 21).

Therefore, much effort has been put into incorporating metabolic data from ^{18}F-FDG PET to improve the accuracy for quantifying tumor burden. The recent evolution in MTV is a good example because it simultaneously contains both anatomic and functional information. Hyun *et al.* first reported that MTV is an independent prognostic factor for survival in addition to TNM stage in patients with EC (14). However, there were greater variations in treatment protocols in their study. Moreover they used the average value of the

optimal threshold SUVs within each quartile group, which was complicated in clinical practice. The heterogeneity and random selection of treatment might have a confounding effect on prognostication. Therefore, validation studies with a more homogeneous population of patients are required. By using a homogeneous treatment modality, our results used two MTV approaches in predicting survival, namely MTV2.5 and MTV20%. The finding was also compatible with our previous study in which we found that a fixed SUV threshold setting of 2.5 (MTV2.5), or an adaptive threshold of 20% of the SUV_{max} (MTV20%) can achieve the optimal correlation in tumor length and conformity index of gross tumor volume (GTV), when applying the auto-contouring function of the SUV threshold in contouring the GTV (16).

The current study was subject to some limitations, such as limited patient number, short follow-up duration and a lack of correlation with pathological tumor length or volume. Nonetheless, substantial evidence showed that the MTVs of primary EC tumors were associated with OS. Because the optimal threshold was always dependent on the PET center, type of malignancy, and tumor characteristics, future MTV studies should enroll more participants prospectively and consecutively, and use standardized protocols for FDG-PET acquisition and partial-volume effect correction. Furthermore, it is also important to adjust for potential confounders such as tumor volume and location to determine the optimal threshold value for this parameter. Based on our data, we recommend that aggressive adjuvant therapy should be considered for patients with EC with a pretreatment MTV2.5>16.0 ml or MTV20%>19.1 ml. Such treatment modification might include adjuvant CRT or chemotherapy. Thus, MTV may become a tool for optimizing the scheme of curative surgery. Furthermore, some improvement of prognostic stratification for patients with EC could be offered by our approach and might lead to a more appropriate selection of suitable candidates for curative surgery.

Conclusion

Besides clinical stage, the pretreatment MTV2.5 or MTV20% can be applied as a prognosticator for patients with EC treated with curative operation. Those with a large MTV should be considered for aggressive adjuvant treatment approaches.

Conflicts of Interest

All Authors declare they encountered no actual or potential conflicts of interest in conducting this study.

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