

Research Article

Prognostic Value of Initial FDG-PET/CT Metabolic Tumor Volume in Patients with Resectable Esophageal Adenocarcinoma

Sonia L. Betancourt^{1*}, Edith M. Marom¹, Diana Palacio¹, Arlene M. Correa² and Wayne L. Hofstetter³

¹Department of Diagnostic Radiology, University of Texas, USA

²Department of Thoracic & Cardio Surgery and Research, University of Texas, USA

³Department of Thoracic & Cardio Vascular Surgery, University of Texas, USA

***Corresponding author**

Sonia L. Betancourt. Diagnostic Radiology, the University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, ZC 77030, Houston, Texas, Tel: 1-713-79293853; Fax: 1-713-794-436139; Email: slbetancourt@mdanderson.org

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Abstract

Objective: Clinical guidelines suggest that pretreatment clinical staging of esophageal adenocarcinoma with ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT) should be used to guide therapy. It is now felt that in the absence of metastatic disease, maximum standard uptake value (SUVmax) on the initial FDG study is poorly predictive of prognosis in patients with locally advanced disease. Perhaps this is because SUVmax accounts for intensity of uptake but not overall tumor burden. We hypothesized that a novel index of image-derived parameters such as metabolic tumor volume (MTV) could be more useful for determining prognosis in patients with esophageal carcinoma.

Methods: A total of 185 consecutive patients who had a pre-treatment FDG PET/CT for esophageal adenocarcinoma treated between 2002 and 2009 with surgery alone (n=62) or neoadjuvant chemoradiotherapy (n=123) were included in this study. Eight different volumetric metabolic models were assessed and compared by Cox regression analyses against other clinicopathological variables of prognostic significance.

Results: By univariate analysis tumor location, preoperative treatment, SUVmax, endoscopic tumor length, clinical stage, and postsurgical stage were significant predictors of survival. On multivariate analysis, clinical stage was the only independent predictive factor associated with overall survival. Most significantly, our analyses, including the use of recursive partitioning revealed that there were no useful FDG PET/CT derived indices for determining prognosis.

Conclusion: Pretreatment SUVmax, and functional tumor uptake measurements were not significant independent prognostic factors for overall survival.

ABBREVIATIONS

AJCC: The American Joint Committee On Cancer; Suvmax: Standardized Uptake Value; FDGPET/CT: ¹⁸F-Fluorodeoxyglucose FDG Positron Emission Tomography; Suvmaxlb: Standardized Uptake Value Lean Body; MTV: Metabolic Tumor Volume.

INTRODUCTION

Esophageal adenocarcinoma is an insidious disease that most often presents in locally advanced to advanced stages. The overall 5-year survival rate in patients amenable to definitive treatment ranges from 5% to 30 [1] but these dependents on stage at

presentation, treatment response, and adequate therapy. It is well recognized that there is substantial outcome heterogeneity among patients with potentially curable esophageal carcinoma, despite current efforts to adequately stage patients. Determining an accurate pretreatment prognosis would be extremely helpful in more appropriately tailoring therapy to either surgery or multimodality treatment. At this time non-invasive staging that includes, FDG PET/CT, computed tomography (CT), esophagogastroduodenoscopy (EGD) and endoscopic ultrasound (EUS) are typically recommended for initial staging. Dedicated CT scans assess local invasion into adjacent mediastinal structures as well as assess for regional lymph node involvement and for

distant metastatic disease. Endoscopy with EUS is an adjunct to CT imaging, and is more capable at detecting depth of invasion and small nodal disease in regional and some non-regional areas accessible by endoscopy. Beginning in 2002 the use of 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET/CT) for staging esophageal cancer has become routine for locally advanced tumors at our institution. PET/CT has been shown to be more sensitive in assessing distant metastases, which can occur in unusual locations often occult to CT [2] and has been shown to change management in more than one third of patients [3].

In addition to the benefits of nodal and metastatic staging, PET/CT provides quantitative data on the amount of FDG uptake by the primary tumor. The most commonly reported index of tumor activity is the maximum standardized uptake value (SUVmax). Although SUVmax has been shown to loosely correspond to stage of disease, it potentially predicts response to therapy in some studies [1]. Our hopes that initial SUVmax would correspond to prognosis and then guide therapy have not been fully realized. Perhaps this is because SUVmax represents only one pixel of FDG activity in the entire tumor rather than assessing the tumor burden. There has been some debate as to whether capturing a volume of FDG avid tissue may be more predictive of prognosis [4]. The thought that volumetric measurements may be associated with outcome stems from knowledge that larger primary tumors have a worse prognosis [5,6]. Measuring the volume of the esophageal malignancy is difficult with morphologic imaging (i.e. CT, MRI, and ultrasound) as the normal tissue surrounding the esophageal malignancy is of similar imaging characteristics and thus separating between the two is fraught with inaccuracies. In a recent publication, it had been suggested that volumetric parameters of FDG uptake represent an independent prognostic factor for survival and are a better predictor of survival than SUVmax [7]. Hatt has reported that a form of volumetric measurement, total lesion glycolysis (TLG) is a promising predictive factor of response to concomitant chemoradiotherapy [8]. The objective of this study was to evaluate the prognostic value for overall survival of several volumetric parameters of FDG uptake in surgical candidates with newly diagnosed esophageal adenocarcinoma. This study is novel in its attempt to utilize pretreatment PET data to more appropriately adjudicate patients to various therapeutic options.

MATERIALS AND METHODS

Patients

For this retrospective study, we reviewed our prospectively maintained database for resected esophageal cancers. Patients who were surgically treated for esophageal adenocarcinoma between March 2003 and January 2009 and had a pretreatment staging FDG PET/CT scan available for review were included in the study. Patient inclusion was limited to 2009 as subsequent to that point imaging algorithms changed which affected our ability to standardize PET/CT derived indices in comparison to scans done pre-2009.

All patients underwent PET/CT, EGD and EUS as part of

the routine for initial staging. In addition, most patients also underwent dedicated contrast CT scans of the chest and abdomen, and some received CT-guided or US-guided biopsies.

Patient PET/CT scans were re-reviewed by a certified thoracic radiologist who was initially blinded to the clinical outcomes. We analyzed the relationship of patient demographics and pretreatment clinical characteristics on outcomes of recurrence and survival status. Because it was infeasible to retrospectively convert our database of clinically staged patients to correspond to a pathologically derived 7th edition staging system, we utilized the originally assigned clinical stage according to the sixth edition of AJCC (American Joint Committee on Cancer) staging system. The overall survival time was calculated as the time from the initial diagnosis to the death date or most recent follow up, in those still alive. This study was approved by the institutional review board of our cancer center (protocol DR09-0761), and we obtained a waiver of informed consent. In addition, our study was in compliance with Health Insurance Portability and Accountability Act regulations.

PET Imaging Parameters

Patient imaging was performed on various scanners at a single institution covering the date range of the selected patients. All scanners were from the same manufacturer (General Electric medical Systems, Milwaukee, NM) and consisted of a D-ST, D-RX, and D-STE PET/CT systems. Patients fasted for at least 6 hours before scanning. Blood glucose levels were measured and were required to be less than 200 mg/dl. Sixty to 90 minutes after administration of 10-15 mCi of 18F-FDG, emission PET images were obtained with two-dimensional mode for 3 minutes per bed position, from head to proximal thigh during shallow breathing. Emission data were corrected for scatter, random events, and dead-time losses using manufacturer's software and images were reconstructed using iterative techniques with and without attenuation correction. To ensure similar image quality between the different scanners used in this study, image reconstruction on all systems was standardized by applying different post smoothing to the resultant images. In addition, all scanners complied with an in-house QA/QC program requiring quarterly calibration and normalization to ensure the accuracy of quantitative measurements. Non-contrast CT images were acquired in helical mode from the base of the skull to the mid thighs during suspended mid-expiration. The CT imaging was performed using 120 kVp, 0.5 sec rotation, pitch of 1.375, with tube current modulation with maximum of 300 mA and a noise index of 20.

Standard and Volumetric PET/CT Image Analyses

PET/CT images were displayed in axial, coronal and sagittal planes and SUVmax (body weight) and SUVmaxlb (lean body) were obtained from a volume of interest encompassing the site of malignancy. In addition, the metabolic tumor volume (MTV) was obtained by delineating a volume of interest using an isocontour with various thresholding techniques: percent SUVmax of 20%, 40%, 60% and 80%. Using this technique, the measured volume includes the area that contains 20% of SUV max and above, 40%

of SUV max and above, and respectively with 60% and 80% (Figure 1). We also grouped measurements as fixed SUVmax thresholds of 2.5, 3.0, 3.5 and 4.0. The volume using this method includes the volume with SUV max of 2.5 and above this value, 3.0 and above, and respectively with 3.5 and 4.0. (Figure 2). All measurements were performed on a GE Advantage workstation using the combined PET/CT images.

Statistical analysis

Multiple Cox's proportional hazards regression models were used to test the statistical significance of several potential prognostic factors for overall survival. The significance of the following factors was tested: age, gender, TNM classification, clinical stage, localization, SUVmax, SUVmaxlb, and MTV by percentage as well as fixed thresholds of the SUVmax. Variable with a p-values of 0.25 or less from the univariate analysis were considered in the multivariate models. A p-value less than 0.05 were defined as significant. Due to issues of co-linearity, the individual MTV techniques were analyzed as separate multivariable models. In situations where a significant p-value was obtained, recursive partitioning was used in an attempt to establish statistically significant cut-off values for PET-based measurements correlating to risk of outcomes. Ultimately, if a model of monotonically increasing hazard ratios could not be established according to degree of uptake or MTV, the model was not considered valid. All of the statistical analyses were performed using SPSS version 17.0.

RESULTS AND DISCUSSION

Results

Demographics: Of the 185 study patients, 163 (88%) were men and 22 (12%) were women. Their ages ranged from 22 to 83 years (mean: 61.0 years). By manner of exclusion, all of the included patients had histologically proven adenocarcinoma, and were treated at a single institution. Surgical resection alone was the primary therapy in 62 patients (33%) and 123 patients (67%) received preoperative chemoradiation (CRT). Surgical resection was by Ivor Lewis type resection in all but a small percentage of cases. Chemotherapeutic agents were typically a platinum doublet utilizing cisplatin and 5-flourouracil. Radiation was administered to a dose of 45-50.4 Gy.

The AJCC pre-treatment clinical disease designation (cTNM) was stage I in 51 patients (28%), stage IIa in 56 patients (30%), stage IIb in 7 patients (4%), stage III in 63 patients (34%), stage IVa in 4 patients (2%), and stage IVb in 4 patients (2%). The location of the tumor was lower esophagus in 182 patients (98.3%; includes distal and GEJ I+II), and in the middle esophagus in 3 patients (1.7%).

PET/CT Parameters: Univariable Cox Regression was used for survival of the total group of 185 patients, for evaluation of clinical and demographic factors as well as the following PET based measurements: SUVmax, lean body maximum standardized uptake (SUVmaxlb), MTV, MTV by percentage (20%, 40%, 60%

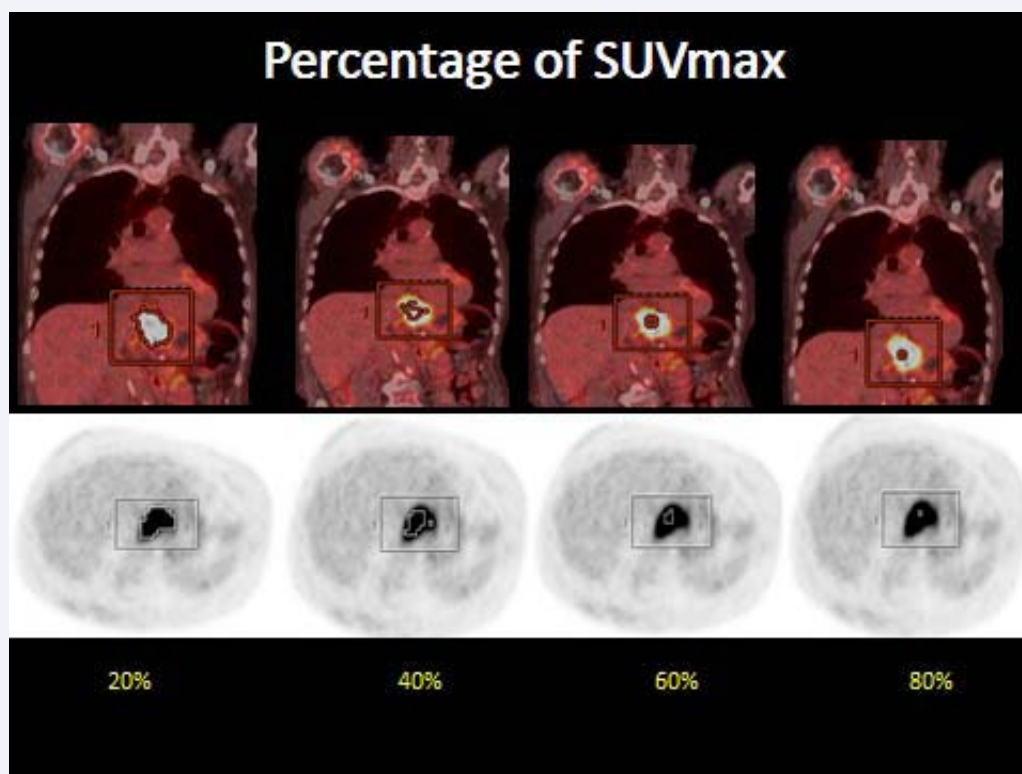


Figure 1 MTV was obtained by automatically delineating the volume of interest using different thresholds 20%, 40%, 60% and 80% of SUVmax. Note that 20% of SUV max represents the largest volume, because includes the volume of 20% of SUV max and above. Consequently 80% is the smallest volume; the volume includes values above of 80% of SUV max.

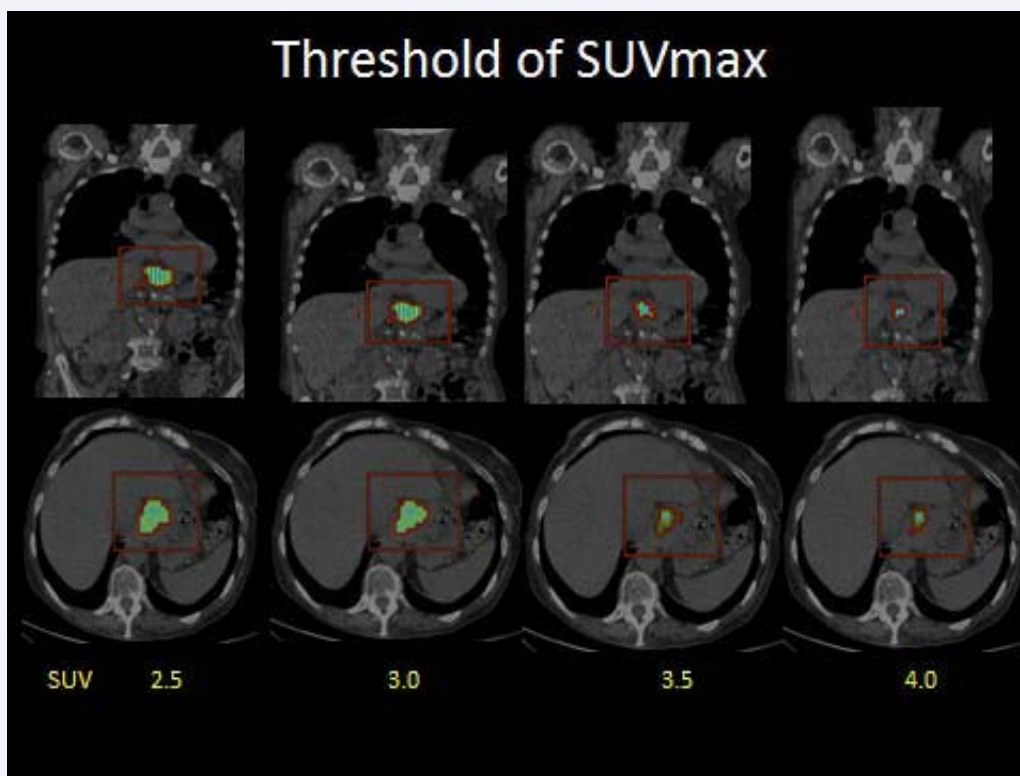


Figure 2 MTV was obtained by delineating the volume of interest using different thresholds. For SUVmax of 2.5, MTV volume represents value SUVmax of 2.5 and above, for 3.0, MTV includes volume of SUVmax of 3.0 and above, and consecutively for 3.5 and 4.0 thresholds.

Table 1: Multivariate Analysis. Variables with significant prognostic value. SUV maxlb shows a significant p-value (0.05), there is no monotonically increasing or decreasing pattern for survival for the different cutoffs values (bold values).

Variable	Frequency	p-value	H.R.	95% C.I. for H.R.		-2 log likelihood
				Lower	Upper	
Clinical Stage		0.003				490.153
1=Stage I (Reference)	51					
2= Stage II	63	0.091	3.558	0.818	15.485	
3= Stage III	63	0.011	6.652	1.546	28.612	
4=Stage IV	8	0.072	5.330	0.859	33.088	
SUV maxlb		0.005				
1.00= <3 (Reference)	41					
2.00= 3-<4	19	0.342	2.436	0.388	15.294	
3.00= 4-<5	19	0.829	1.249	0.167	9.359	
4.00= 5-<6	18	0.055	5.705	0.961	33.879	
5.00= 6-<7	15	0.416	2.157	0.339	13.742	
6.00= 7-<9	20	0.254	2.882	0.468	17.769	
7.00= 9-<10	7	0.770	0.679	0.051	9.048	
8.00= 10-<11	6	0.008	12.251	1.951	80.332	
9.00= 11-<13	9	0.444	2.199	0.292	16.550	
10.00= 13-<15	10	0.201	3.494	0.514	23.762	
11.00= 15-<25	10	0.627	0.527	0.040	6.981	
12.00= >=25	11	0.042	7.109	1.076	46.966	

Abbreviations: H.R.: Hazard ratio; C.I.: Confidence Interval; EUS: Endoscopic Ultrasound; PET/CT: ¹⁸F-fluorodeoxyglucose FDG Positron Emission Tomography; SUVmax: Standardized Uptake Value; SUVmaxlb: Standardized Uptake Value lean body; MTV: Metabolic Tumor Volume.

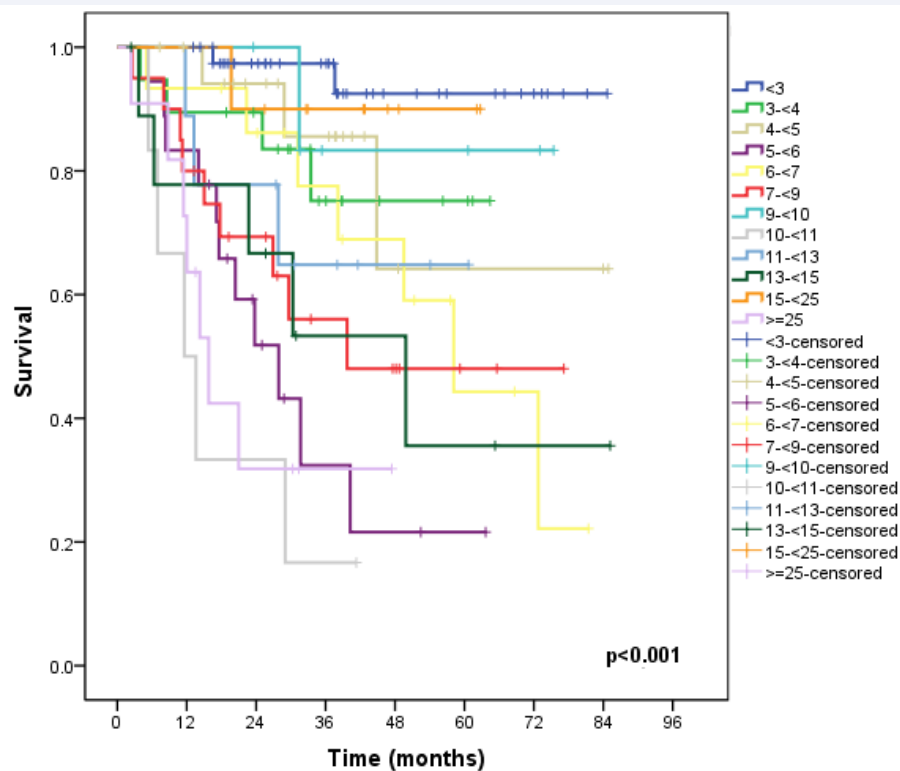


Figure 3 SUVmaxlb was statistically significant after multivariate analysis (p-value 0.005), unfortunately, the cutoffs obtained using recursive partitioning did not show a monotonically increasing or decreasing pattern for survival.

and 80%) and by fixed thresholds of the SUV max (2.5, 3.0, 3.5, and 4.0). For each of the PET-based measurements cut-offs were obtained using recursive partitioning. All the PET-based measurements had p-value < 0.05 except MTV (p=0.200).

For each of them a Multivariate Cox Regression was performed including tumor location, preoperative treatment, clinical stage, tumor length, and PET-based measurement. For most of the models only clinical stage remained significant, except some models in which in addition to the clinical stage, the PET based measurements remained significant: SUVmaxlb, PercentSUVmax20, PercentSUVmax40, Percent SUVmax 60, percent SUVmax80, threshold 2.5, and threshold 3.5. Of all of the models in which the PET based measurement remained in the model, the SUVmaxlb group obtained the lowest -2 log likelihood of being a potential useful prognostic variable (Table 1, Figure 3). Unfortunately, the results obtained using recursive partitioning did not provide us with a monotonically increasing or decreasing pattern for survival that would be required for this to be a clinically useful prognostic parameter.

Given that there is some heterogeneity of the patient cohort in this study we decided to perform a subgroup analysis. We separated our data by patients who received neoadjuvant therapy and those who proceeded directly to surgery, 123 and 62 patients respectively. For the 62 patients that were treated with surgery alone, the univariate analyses showed a significant association with overall survival for: SUVmax (p= 0.001), SUVmaxlb

(p=0.004), MTV (p= 0.001), age (p=0.007), clinical stage (p=0.001), and maximal tumor length as assessed by endoscopic ultrasound (0.007). For the PET measurements, SUVmax (p=0.011), SUVmaxlb (p=0.005), MTV (p=0.004) were significant. On multivariable analysis none of the PET-based measurements were associated with overall survival. The univariate and multivariate analysis for patients who received neoadjuvant therapy (n=123) included the same clinical, demographic factors and PET measurements; again none of the PET measurements remained in the final model as an independent prognostic variable.

Discussion

Accurate staging is essential in directing patients to appropriate therapy, unfortunately pretreatment prognostic factors are currently lacking, and our inability to derive a precise pretreatment stage is well described, to the point that some reports recommend invasive staging. This has unfortunately lead to "lumping" patients with very disparate survival potential into treatment categories that may or may not be appropriate. PET/CT has been shown to have an important role in the staging of esophageal carcinoma and has been increasingly used to determine the presence of otherwise undetected metastatic disease [4, 21-26]. It is felt, however, that the utility of FDG/PET could go beyond the detection of metastases and that the uptake intensity on the initial diagnostic study may be prognostic. In fact, the association between the highest measured standardized

uptake value (SUVmax) on the initial diagnostic FDG/PET and prognosis has been studied. One such study assessing the SUVmax predictive capability in clinical early staged esophageal adenocarcinoma showed that SUVmax could predict survival, with lower FDG uptake associated with improved survival, compared to those with higher FDG uptake who had a higher likelihood of having advanced disease at final pathologically staged disease [2]. In contrast, another study found that for patients with locally advanced esophageal adenocarcinoma, initial SUVmax did not predict survival but a high SUVmax was associated with better response to preoperative therapy [1]. Recently, Al-Taan reported that SUV max is closely linked to disease state, but it doesn't represent a useful prognostic factor in any stage [3]. Due to the fact that current results are conflicting, it would seem that initial SUVmax is not a reliable measure of prognosis in the clinical setting. There has been some debate as to whether capturing a volume of FDG avid tissue may be more predictive of prognosis [4]. SUVmax represents only one pixel of FDG activity in the entire tumor, perhaps employing the addition of tumor burden to a conglomerate measurement would improve the prognostic ability of FDG/PET. Evaluation of volumetric metabolic measurements in esophageal carcinoma could be potentially useful for stratification of patients to the correct therapy as there is often underestimation of disease by clinical staging.

There is supportive data in the literature for this concept; it is known that prognosis is affected by tumor volume. Longer tumors are associated with worse overall survival [5,6]. Some authors have proposed assessing tumor longitudinal length based on 18 F-FDG PET images as a predictor of response to therapy and survival [8-10]. Hyun et al reported a retrospective study of 151 patients concluding that MTV is an important independent prognostic factor for survival and a better predictor of survival than SUVmax for the primary tumor in patients with esophageal carcinoma [11].

Our study comprises the largest study on metabolic volume assessment in esophageal adenocarcinoma. Unfortunately, initial SUVmax of the primary tumor was not a significant independent prognostic factor for overall survival. Our results also indicate that we were not able to demonstrate any association between metabolic tumor volume and overall survival. Despite the fact that the values themselves were statistically significant in the model, the use of recursive partitioning revealed that there were no useful cut-offs for determining prognosis, and the hazard functions were neither ordered nor monotonal. While a study may find a statistical correlation of SUV value to outcome, these values must be meaningful (ordered) to result in a clinically useful parameter that would guide therapy.

Manual volumetric measurements are not only cumbersome and labor intensive, but also suffer from greater inter observer variability than automated volumetric measurements [12]. Variability in measurement intensifies when tumor borders are indistinct. Erasmus et al reported that CT measurement of tumor volume requires that the tumor margin be outlined

on each axial image. A potential inherent limitation of this technique when poorly defined lesions are evaluated is that the accuracy of the tumor delineation depends on either subjective determination of tumor margins or computer software that uses tissue segmentation techniques [13]. In esophageal cancer, where normal tissue and the tumor have the same soft tissue density an accurate delineation of the lesion is difficult. Thus, using an automated volumetric physiologic type imaging that analyzes FDG uptake rather than the morphology of the tumor itself would theoretically be ideal in overcoming the limitations to linear measurements of non-spherical tumors. However, an ideal method of measuring volumes has yet to be found, and all volumetric uptake measurements are more cumbersome than measuring one point of maximal FDG activity. Perhaps this is a reason that this method has thus far been for the most part avoided.

The esophagus, embedded in the mediastinum, is surrounded by mediastinal structures. The digestive organs themselves (esophagus and stomach) and the mediastinal structures display background FDG avidity which is often similar to the activity found in malignant lesions. Separating the tumor from surrounding normal activity could be problematic for volumetric measurement. Therefore, methods needed to be devised to account for tumor versus normal tissues. If one employs a low threshold, for example a low percentage of SUVmax (i.e. 20%) or a low fixed threshold (i.e. SUV 2.5), metabolic volumes are higher and are more likely to include normal surrounding tissues. On the other hand, utilizing a high threshold (i.e. 80% of SUVmax or fixed threshold of 4.0) could result in eliminating FDG avid tumor volume. To overcome this issue we stratified our study using multiple thresholds, yet, none of these spectra of threshold correlated with outcome.

Our study has several limitations. First, we evaluated the SUVmax and volume of the primary malignancy, though tumor burden in addition to the primary tumor, includes, regional lymph nodes and distant metastases. Indeed, data supports that the number of involved lymph nodes is an independent predictor of long-term survival in esophageal and gastroesophageal junction tumors [14-16]. A recent study suggest that PET/CT detected nodal metastasis is an independent preoperative risk factor for postoperative recurrence [17,18]. Our study population however was only composed of surgical patients. Thus none had distant metastases. The majority of the locoregional lymph node disease was actually included in the tumor measured as in the majority of patients it was impossible to separate the FDG activity arising from the primary tumor itself and the periesophageal lymph nodes abutting it secondary to a halo effect. For those lymph nodes distant from the primary tumor, because of their small size, their FDG activity as measured by PET/CT is underestimated. This is primarily due to partial volume effects (PVE) whereby the underestimation of activity concentration in lesions below PET/CT image resolution has been well documented [19]. Thus, in our specific patient population, that is, in surgical candidates, with low volume locoregional spread, all patients' measurements were performed in the same fashion. However, our results are

limited to this patient population and cannot be translated to patients with more advanced disease. The second limitation to our study has to do with the inaccuracies pertaining to measuring FDG uptake. SUV is inaccurate to the extent that it is affected by multiple factors including partial volume, noise, time between tracer injection and imaging, attenuation correction, glucose level and respiratory motion [11, 20-22]. Hatt et al reported that the level of reproducibility in measuring functional tumor volume (TV) from 18 F-FDG/CT imaging can vary from 21 to 90% using automatic and thresholds-based approaches respectively [9, 23].

Finally, we acknowledge that there are several variables that are known to be prognostic that were not included in this study. Factors such as treatment response, pTNM, and pathologic complete response are not pretreatment variables, nor are these data available to the clinician when formulating a treatment plan. The purpose of this study was to validate the concept that initial PET parameters could differentiate prognosis of patients suffering from esophageal adenocarcinoma, and therefore potentially aid in guiding therapy. Along those lines, the primary conclusion of this manuscript is not centered on the finding that cTNM is an independent prognostic variable; rather it is the finding that initial staging PET parameters are not prognostic, even when expanded to novel volumetric methods of SUV measurement.

CONCLUSION

We conclude that whereas PET/CT is a powerful tool that provides staging information that potentially changes the management in patients with esophageal carcinoma by detection of metastatic disease, the prognostic value of PET image-derived parameters such as SUVmax and metabolic tumor volume is not clear. The potential use of these and other factors as predictors of response to therapy and overall survival is a topic of great interest.

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