

# Prognostic Value of <sup>18</sup>F-FDG PET/CT Metabolic Tumor Volume for Complete Pathologic Response and Clinical Outcomes after Neoadjuvant Chemoradiation Therapy for Locally Advanced Esophageal Cancer

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## Abstract

**Purpose/Objective:** The prognostic value of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) has not yet been defined in locally advanced esophageal cancer (LAEC). This study aims to elucidate the prognostic role of PET/CT for patients treated with neoadjuvant chemoradiation (CRT) followed by esophagectomy.

**Materials/Methods:** We retrospectively evaluated patients with LAEC treated from 2006 to 2014 with neoadjuvant CRT followed by esophagectomy. A 76 patients had pre-CRT and post CRT PET/CT scans. PET parameters maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), peak standardized uptake value (SUVpeak), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were recorded for both pre-CRT and post-CRT scans. The correlation of the measured parameters with pathologic complete response (pCR) and clinical outcomes was analyzed.

**Results:** Receiver operating characteristic (ROC) analysis was performed to determine the optimal cutoff values for predicting pCR. Binomial logistic regression using these optimal cutoff values was performed for pCR. A pre CRT MTV <33.1 was 4 times more likely to have a pCR (OR 4.20 95%CI 1.60 to 11.0, p=0.004). Pre CRT TLG <153 was 4.7 times more likely to have a pCR (OR 4.71 95%CI 1.78 to 12.4, p=0.002), and post CRT TLG <53.1 was 4.5 times more likely to have a pCR (OR 4.52 95%CI 1.60 to 12.7, p=0.004). On MVA, pre-CRT MTV and pre CRT TLG remained significant (p=0.006 and p=0.039, respectively). Percent change in MTV independently predicted for OS (p=0.034). By contrast, SUVmax and SUVpeak did not predict for pCR or survival.

**Conclusions:** Pre CRT MTV and pre CRT TLG were independently predictive of pCR, and percentage change in MTV independently predicted for OS in LAEC. Further study is needed to determine if MTV and TLG values can help define which patients will most benefit from radiation dose escalation and esophagectomy.

**Keywords:** Metabolic tumor volume; Total lesion glycolysis; <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography; Pathologic complete Response; Locally advanced esophageal cancer; Chemoradiation therapy; Neoadjuvant therapy; Multimodality management

## Introduction

In 2015 there were approximately 17,000 estimated new esophageal cancers diagnosed and nearly 16,000 estimated deaths in the United States [1]. While the incidence of squamous cell carcinoma (SCC) has declined likely due to significant reductions in smoking and alcohol consumption, the incidence of adenocarcinoma (AC) has been rising due to increasing gastroesophageal reflux disease and obesity [2]. The majority of esophageal cancer patients present with locally advanced or metastatic disease, and the five-year survival rate remains dismal at 18% [1]. To improve outcomes in locally advanced esophageal cancer (LAEC), treatment modality has shifted from surgery alone to trimodality therapy with neoadjuvant chemoradiation (CRT) [3]. The CROSS trial, in particular, was the largest randomized trial demonstrating an overall survival advantage to CRT followed by surgery when compared to surgery alone, establishing this approach as a standard of care in LAEC [4].

However, the value of resection after CRT remains controversial. Two randomized trials demonstrated no survival benefit with the addition of surgery to CRT in SCC of the esophagus [5,6]. However, both

studies also demonstrated local failure rates near 50% with CRT alone with significant improvement in local control with surgical resection following CRT. A phase II trial comparing CRT with or without surgery in AC of the esophagus also showed no difference in overall survival or cause specific survival. Local failure was higher in patients undergoing CRT alone; however, surgical salvage resulted in similar overall local control between the two groups [7]. Furthermore, the morbidity of esophagectomy after CRT is significant, exceeding 30% in some reports [8] with profound quality of life and medical cost implications. Given this mixed evidence regarding the benefit of surgery following CRT in LAEC, accurate assessment of response to CRT could potentially

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guide treatment decisions by identifying a set of patients who can safely forego esophagectomy, or conversely, which patients may benefit from treatment intensification.

Following neoadjuvant therapy, clinicians most commonly rely on 3D <sup>18</sup>F-Fluorodeoxyglucose (FDG) PET/CT to assess response. There have been multiple studies demonstrating the correlation between FDG activity and metabolic and pathological tumor response [8-12], but the ideal metabolic parameters to assess response have not been well established, and results are inconsistent. For example, Vallböhmer et al. [13] evaluated 119 patients treated with CRT followed by esophagectomy who underwent pre and post CRT PET/CT and found no significant association between maximum standardized uptake value (SUVmax), pre or post CRT, with histomorphologic response or survival, and the receiver operating characteristic (ROC) analysis could not identify a SUV threshold with a relevant predictive value for histomorphologic response [13]. Conversely, Swisher et al. [14] found a significant correlation between post CRT SUVmax and both pathologic response and survival in 103 patients with LAEC.

Given these discordant results, recent retrospective studies have focused on exploring the prognostic potential of other metabolic parameters besides SUVmax, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG). MTV pre CRT has not only been shown to be an independent prognostic factor for survival but also, a superior predictor of survival than SUVmax in LAEC [15-21]. Li et al. [22] found sequential SUVmax, MTV and TLG to be similarly predictive of overall survival. One study found MTV and TLG pre CRT to be predictive of pathologic response as determined by biopsy [19,20]. Another study [23] found that MTV and TLG post CRT predicted for pathologic response as determined by surgical specimens and survival, while two studies [24,25] found the change in MTV to be predictive of pathologic response and survival, but had conflicting results regarding the prognostic value of TLG. Conversely, two studies [26,27] found TLG to be the best PET/CT predictor of survival.

One prospective trial has evaluated the predictive value of PET/CT parameters prior to CRT and on day 21 of CRT and found baseline MTV, TLG and SUVmax to be predictive of response, while PET/CT on day 21 of CRT appeared to have less clinical relevance [28]. A second prospective trial found no association between pathologic response and any PET/CT parameters prior to CRT, during CRT or post CRT [29]. Of note, a variety of methods for delineating MTV were utilized in these studies including qualitative and visual assessment, fixed SUV threshold values ranging from 2.0-6.5, and SUV threshold values as a percentage of the SUVmax.

A more reliable assessment of response to CRT may help guide treatment decisions. The purpose of this study is to determine which PET parameters are the most predictive of pathologic response and survival after neoadjuvant CRT for esophageal cancer.

## Materials and Methods

### Patient population

After Institutional Review Board approval, a radiation oncology database was retrospectively queried to identify non-metastatic esophageal cancer patients treated with intensity modulated radiation therapy (IMRT) at our institution from 2006 to 2014. Only patients treated with concurrent CRT followed by esophageal resection were included in this study. Patients who underwent induction chemotherapy were excluded. A total of 113 were identified. Of this group, 76 had pre

CRT and post CRT <sup>18</sup>F-FDG PET/CT scans performed at our institution and were included in this study.

### Treatment

All patients underwent neoadjuvant CRT followed by esophagectomy. The majority of patients (63/76, 83.0%) received concurrent cisplatin (75 mg/m<sup>2</sup> on day 1 and day 28) and protracted venous infusion 5-fluorouracil (225 mg/m<sup>2</sup> weekly) [30]. The remaining 13 patients received a variety of concurrent chemotherapy regimens at the discretion of the treating medical oncologist. All patients were treated with IMRT by the same 2 radiation oncologists who specialize in the treatment of gastrointestinal (GI) malignancies. All patients were referred for EUS-guided fiducial placement to delineate the esophageal tumor volume using a previously described technique [31]. A 4D CT-based planning was utilized to account for respiratory motion. Daily image guidance with cone beam CT (CBCT) was performed to ensure that the fiducial markers were appropriately aligned.

Patients were either treated to a dose of 50.4 Gy in 1.8 Gy fractions to the tumor and regional lymphatics or with dose-painted IMRT (dp-IMRT) where 50.4 Gy in 1.8 Gy fractions was delivered to regional microscopic lymphatics while simultaneously delivering 56 Gy in 2 Gy fractions to gross disease. Patient selection for treatment with 50.4 Gy or dp-IMRT 50.4/56 Gy was nonrandom and not performed on protocol.

### Pathologic assessment

All pathologic assessment was performed on surgical specimens analyzed by site-specific gastrointestinal pathologists. Pathologic response was given as complete response (pCR), partial response (pPR) and no response (pNR). Tumor regression grading (TRG) was also performed using the TRG scale adopted by the College of American Pathologists [32]. TRG 0 indicates no viable cancer cells (complete response). TRG 1 indicates single cells or small groups of cancer cells (moderate or near complete response). TRG 2 indicates residual cancer outgrown by fibrosis (minimal response). TRG 3 indicates extensive residual cancer (no response).

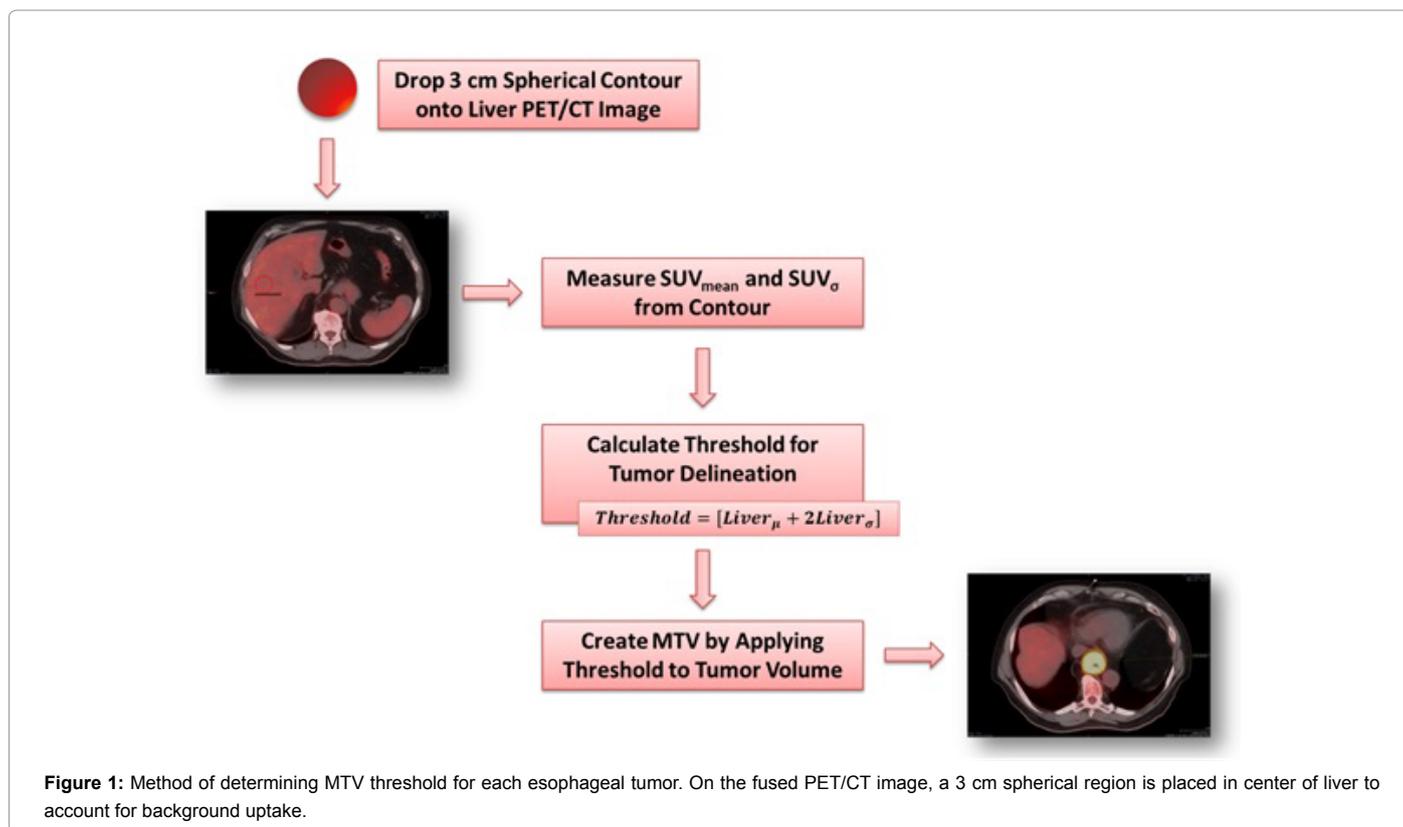
### <sup>18</sup>F-FDG PET/CT acquisition

Patients were scanned with a Discovery VCT PET/CT system (GE Medical Systems) before and after receiving CRT. All patients were imaged according to the standard procedures at our institution where patients are instructed to fast for 6 h prior to injection of FDG (10 mCi/370 MBq). If the blood glucose level is above 200 mg/dL, unless this is the patient's baseline, the scan will not be performed that day. After FDG injection, patients then underwent a 90 min uptake period prior to the scan according to the Society for Nuclear Medicine and Molecular Imaging (SNMMI) guidelines.

### Measurement of metabolic parameters

PET/CT images were imported into an image analysis software system (Mirada RTx, Mirada Medical, Oxford, UK). Pre and post CRT PET/CT images were registered with a proprietary automatic rigid registration followed with a fine, CT deformable image registration. A volume of interest (VOI) was created using the Dholakia method – an adaptive threshold method to account for background uptake (Eq. 1) [33]. A 3 cm spherical region of interest (ROI) was placed in a uniform region of the liver. The mean value and standard deviation of the SUV within the spherical ROI were extracted to calculate a threshold for the VOI contour (Figure 1):

$$\text{Threshold}=[\text{Liver}\mu+2\text{Liver}\sigma] \quad (1)$$



where  $\mu$  is mean and  $\sigma$  is standard deviation. Contours encompassing the volume of tumor within the esophagus with metabolic activity greater than or equal to this calculated threshold value were drawn on pre and post CRT PET/CT images (Figure 2), and a Boolean tool was used to avert areas of high uptake from the heart or the stomach. These contours were then physician edited and/or verified. Once physician approved, these contours were deemed the volumes of interest (VOI).

The following PET parameters were extracted from the VOI of both pre CRT and post CRT scans: SUVmax, peak standardized uptake value ( $SUV_{peak}$ ), MTV, mean standardized uptake value ( $SUV_{mean}$ ), and standardized uptake value standard deviation ( $SUV_{\sigma}$ ). Total lesion glycolysis (TLG) was defined as MTV multiplied by  $SUV_{mean}$ . Percent reduction of SUV max,  $SUV_{peak}$ , MTV and TLG was defined as (pre CRT value – post CRT value)/(pre CRT value)  $\times$  100.

### Statistical analysis

Patient, tumor and treatment characteristics were compared between pCR and pPR/pNR groups using Pearson Chi Square. Receiver operating characteristic (ROC) analysis was performed using PET parameters in order to determine a binomial cutoff value that would optimally predict pathologic response. Median values were obtained for all PET parameters if ROC curves were not significant. Univariate analysis (UVA) was performed using binomial logistic regression to determine the predictability of these optimal cutoff and median values on pathologic response. All significant variables ( $p < 0.05$ ) were included on multivariate analysis (MVA) via logistic regression analysis, with statistical significance defined as  $p < 0.05$ . Clinical outcomes including local regional control (LRC), distant metastasis (DM), freedom from failure (FFF), disease free survival (DFS), and overall survival (OS) were defined from date of pathological diagnosis and were estimated

using the Kaplan-Meier method. Mantel-Cox log rank analysis was performed to evaluate the effect of PET parameters on these clinical outcomes. Values significant on UVA ( $p < 0.05$ ) were then run on a MVA via Cox-regression analysis. Two-sided p-values and the level of significance of 0.05 were used for statistical analyses and all analyses were performed using SPSS v 23 (IBM, Armonk, NY).

### Results

Patient, tumor and treatment characteristics separated by pCR vs pPR/pNR are compared in Table 1. The median patient age of the entire cohort was 65. Of the 76 patients, 63 (83.0%) had ACC, and the remaining 13 (17%) had SCC. The majority of tumors (65, 85.5%) were located in the distal esophagus or gastroesophageal junction (GEJ). Standard IMRT to 50.4 Gy was utilized in 23 (30.1%) patients, while dp-IMRT to 56 Gy was delivered to the other 53 (69.7%) patients. All patients had negative margins following esophagectomy. Based on pathologic response, 37 (49%) patients were classified as the pCR group, and 39 (51%) patients were classified as the pPR/ pNR group. Similarly, 59 (77.6%) patients were classified as the TRG 0/1 group and 17 (22.4%) patients were classified as the TRG 2/3 group. The mean interval from the baseline PET/CT to the initiation of CRT was 21 days (4-52). The mean interval from the end of CRT to the post-Tx PET/CT was 41 days (21-83). The mean interval from the end of CRT to surgical resection was 81 days (38-152). The only significant differences between patients who underwent a pCR and those who did not were radiation dose, lymphovascular space invasion (LVSI) and interval between completion of CRT and restaging PET/CT. Patients treated to 56 Gy as compared to 50.4 Gy were more likely to undergo a pCR ( $p = 0.04$ ), and patients in the pPR/pNR group were more likely to have LVSI ( $p = 0.001$ ) and had a shorter mean interval from end of CRT to restaging PET/CT of 2 days ( $p = 0.04$ ).

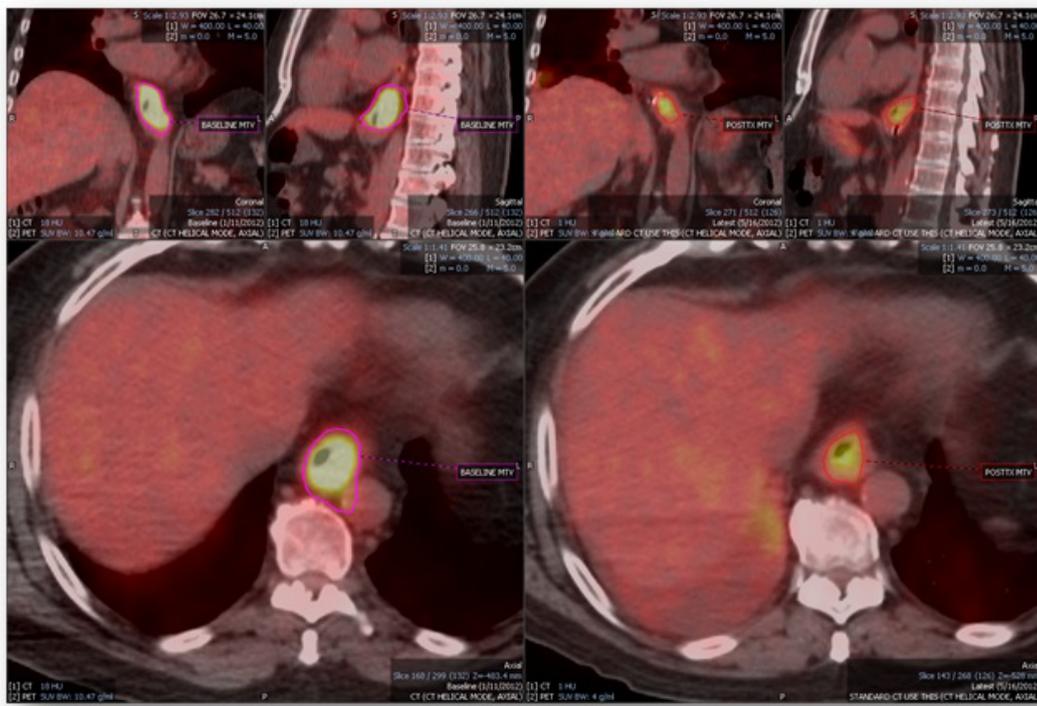


Figure 2: Left: Baseline MTV; Right: Post Tx MTV.

ROC curve analysis was performed to assess the AUC and determine the optimal cutoff values for predicting pCR. Lower MTV prior to CRT predicted for pCR at an optimal cutoff of 33.1 with a sensitivity of 71.8% and a specificity of 62.2% (AUC of 0.690,  $p=0.004$ ) (Figure 3). MTV after CRT also predicted for pCR at an optimal cutoff of 10.7 with a sensitivity of 59.0% and a specificity of 62.2% (AUC of 0.640,  $p=0.036$ ) (Figure 3). Pre CRT TLG and post CRT TLG also predicted for pCR. Pre CRT TLG, at an optimal cutoff of 153, predicted for pCR with a sensitivity of 64.9% and a specificity of 71.8% (AUC of 0.679,  $p=0.007$ ) (Figure 3). Post CRT TLG predicted for pCR at an optimal cutoff of 53.1 with a sensitivity of 81.1% and specificity of 51.3% (AUC 0.645,  $p=0.029$ ) (Figure 3). Binomial logistic regression using these optimal cutoff values was performed for pCR. A pre CRT MTV <33.1 was 4 times more likely to have a pCR (OR 4.20 95%CI 1.60 to 11.0,  $p=0.004$ ). Post CRT MTV <10.7 was twice as likely to have a pCR (OR 2.37 95%CI 0.940 to 5.93,  $p=0.067$ ), approaching significance. Pre CRT TLG <153 was 4.7 times more likely to have a pCR (OR 4.71 95%CI 1.78 to 12.4,  $p=0.002$ ), and post CRT <53.1 TLG was 4.5 times more likely to have a pCR (OR 4.52 95%CI 1.60 to 12.7,  $p=0.004$ ). By contrast, SUVmax and SUVpeak before or after CRT did not significantly predict for pCR. Percent change of SUVmax, SUVpeak, MTV and TLG also did not predict for pCR. None of the PET parameters were able to significantly predict for TRG 0/1 versus TRG 2/3. Median values were obtained for all MTV measurements if ROC curves were not significant. None of the median values were predictive of pCR or TRG 0/1.

UVA was performed using binomial logistic regression to assess which factors influenced pCR outcome. Age, gender, histology, tumor length, tumor location, T stage, N stage, AJCC 7<sup>th</sup> edition stage, radiation dose, margin status, LVSI, and PET/CT parameters were included. Radiation dose ( $p=0.04$ ), LVSI ( $p<0.0005$ ), pre CRT MTV ( $p=0.004$ ), pre CRT TLG ( $p=0.002$ ), and post CRT TLG ( $p=0.004$ ) were all significant. Since MTV and TLG are related, two separate MVAs

were performed with all variables significant on UVA. On the MTV MVA, only pre-CRT MTV remained significant (OR 4.00 95%CI 1.48 to 10.6,  $p=0.006$ ). On the TLG MVA, only pre CRT TLG remained significant (OR 2.90 95%CI 1.06 to 8.17,  $p=0.039$ ).

UVA and MVA were performed with the same variables and TRG as the outcome. Radiation dose of 56 Gy ( $p=0.005$ ) and no LVSI ( $p<0.0005$ ) both predicted for a TRG 0/1 on UVA. Both remained significant on MVA with patients receiving a dose of 56 Gy having a 6 times higher chance of having a TRG 0/1 (OR 6.10 95%CI 1.71 to 25.0,  $p=0.008$ ), and patients with no LVSI having a 16 times higher chance of having a TRG 0/1 (OR 16.0 95%CI 2.91 to 83.9,  $p=0.001$ ).

Kaplan Meier curves were generated to correlate median values of PET parameters to LRC, DM, FFF, DFS and OS. Percent reduction of MTV >69% (median value) predicted for improved OS (HR 2.18 95%CI 1.00 to 4.74,  $p=0.045$ ) (Figure 4). None of the other PET parameters predicted for recurrence or survival outcomes. Univariate cox regression was performed to assess which patient, tumor, treatment and PET/CT variables impacted recurrence and survival outcomes. All significant variables were included in a MVA. Only radiation dose of 56 Gy significantly predicted for locoregional control (OR 9.20 95%CI 1.09 to 77.3,  $p=0.014$ ). Only clinical N stage predicted for DM (OR 11.0 95%CI 1.31 to 91.9,  $p=0.005$ ) and DFS (HR 5.90 95%CI 1.59 to 22.0,  $p=0.003$ ). Finally, clinical N stage (HR 5.10 95%CI 1.06 to 5.10,  $p=0.016$ ) and % MTV change (HR 2.30 95%CI 1.36 to 18.9,  $p=0.034$ ) independently predicted for OS. ROC analysis, UVA and MVA correlating PET/CT parameters to pCR and OS are summarized in Table 2.

## Discussion

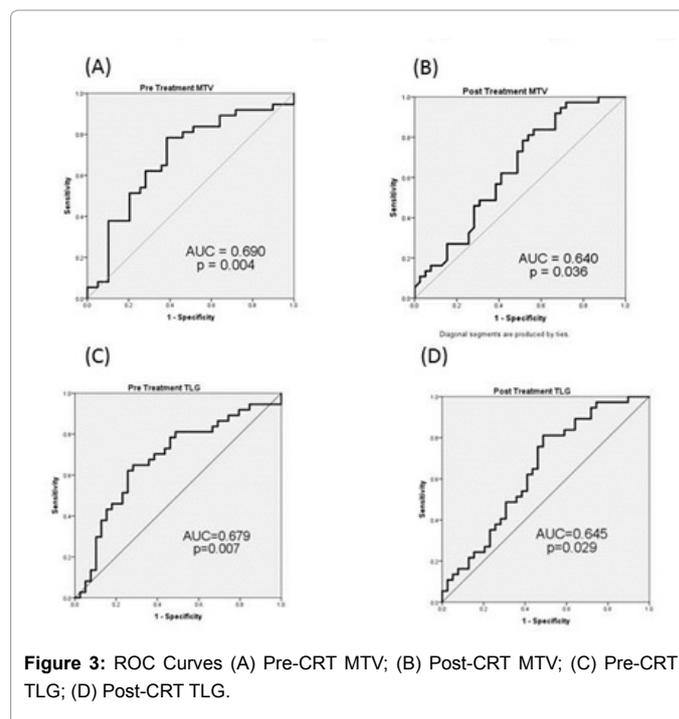
This is the largest study to evaluate the prognostic value of pre and post CRT MTV and TLG on pathologic response and survival in LAEC treated with neoadjuvant CRT followed by esophagectomy. Our

study retrospectively evaluates and compares the prognostic value of PET/CT parameters pre and post CRT, as well as the percent change of these values in 76 patients. After accounting for patient, tumor and treatment characteristics, we found that pre CRT MTV and pre CRT TLG independently predict for pCR, and that % change in MTV independently predicts for OS. Of note, SUVmax and SUVpeak did not correlate with pathologic response or survival, and no PET/CT parameters predicted for TRG 0/1.

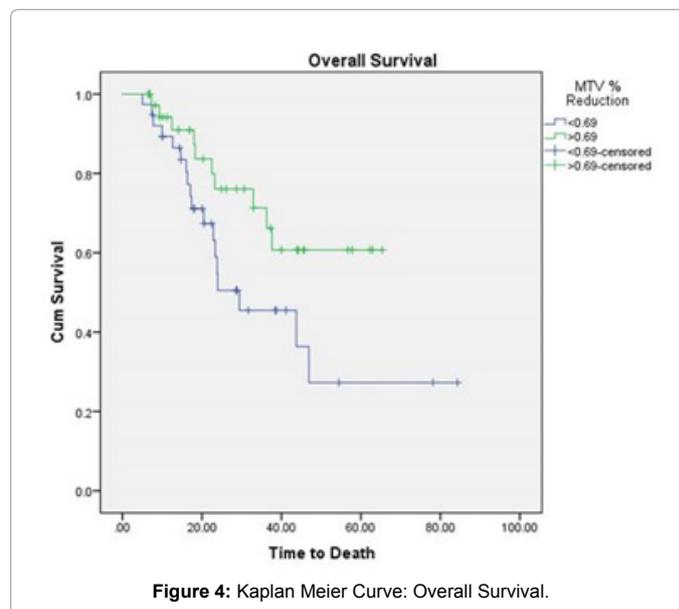
Although this study is retrospective in nature with the well-established ensuing biases, all the PET/CT scans were obtained at a single institution, utilizing the same protocol, limiting discrepancies in acquisition. Furthermore, we chose to use the Dholakia method to calculate our VOI from which to abstract PET/CT parameters. This adaptive method is easily reproducible and accounts for individual patient variance in background SUV uptake. In addition, the

CHARACTERISTIC	All n (%)	pCR	pPR/pNR	p-value
<b>AGE</b>				
<65	43 (56.6)	20	23	0.655
>65	33 (43.4)	17	16	
<b>GENDER</b>				
Male	61 (80.3)	31	30	0.453
Female	15 (19.7)	6	9	
<b>HISTOLOGY</b>				
Adenocarcinoma	63 (82.9)	30	33	0.683
Squamous Cell Carcinoma	13 (17.1)	7	6	
<b>LOCATION OF TUMOR</b>				
Upper	3 (3.95)	2	1	0.266
Middle	8 (10.5)	5	2	
Lower	37 (48.7)	20	18	
GEJ	28 (36.8)	10	18	
<b>CLINICAL T STAGE</b>				
T1	1 (1.31)	1	0	0.176
T2	14 (18.4)	10	4	
T3	53 (69.7)	23	30	
T4	8 (10.5)	3	5	
<b>CLINICAL N STAGE</b>				
N0	18 (23.7)	12	6	0.217
N1	44 (57.9)	19	25	
N2	14 (18.4)	6	8	
<b>TNM STAGE (7<sup>th</sup> Edition)</b>				
IB	1 (1.31)	2	1	0.239
IIA	3 (3.95)	3	1	
IIB	21 (27.6)	14	7	
IIIA	34 (44.7)	12	20	
IIIB	10 (13.2)	3	6	
IIIC	7 (9.21)	3	4	
<b>DOSE to GTV</b>				
50.4 Gy	23 (30.3)	7	16	0.04
56 Gy	53 (69.7)	30	23	
<b>Lymphovascular space invasion (LVSI)</b>				
Present	10	0	10	0.001
Absent	66	37	29	
Mean Days from Initial PET to CRT (range)	21.1 (4-52)	21.11	21.03	0.509
Mean Days from CRT to restaging PET (range)	41.5 (21-83)	42.22	40.74	0.04
Mean Days from CRT to Surgery (range)	81.0 (38-152)	83.22	78.92	0.665

**Table 1:** Patient, tumor, and treatment characteristics compared by pathologic response.



**Figure 3:** ROC Curves (A) Pre-CRT MTV; (B) Post-CRT MTV; (C) Pre-CRT TLG; (D) Post-CRT TLG.



**Figure 4:** Kaplan Meier Curve: Overall Survival.

treatment was homogeneous with all patients receiving concurrent chemoradiotherapy with IMRT followed by esophagectomy. Finally, pathologic response was determined by site specific gastrointestinal pathologists, based on surgical specimens, the established gold standard for response determination. Of note, however, our study included patients with SCC and ACC, the timing of PET/CT scans varied in relation to CRT, and patients were treated to two different radiation doses.

These results add to the growing body of literature exploring the prognostic implications of PET/CT parameters in esophageal cancer. A number of studies have previously evaluated baseline MTV values with survival outcomes in esophageal cancer. Shum et al. [18] evaluated 26 patients with SCC of the esophagus who underwent PET/CT prior

Variable	Response (pCR)								Overall Survival (OS)			
	ROC			UVA		MVA			UVA		MVA	
	Cutoff	AUC	p	OR (95%CI)	p	OR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	
MTV pre-CRT	33.1	0.69	<b>0.004</b>	4.20 (1.60-11.0)	<b>0.004</b>	4.00 (1.48-10.6)	<b>0.006</b>	-	0.611	-	-	
MTV post-CRT	10.7	0.64	<b>0.036</b>	2.37 (0.940-5.93)	0.067	-	-	-	0.702	-	-	
TLG pre-CRT	153	0.679	<b>0.007</b>	4.71 (1.78-12.4)	<b>0.002</b>	2.90 (1.06-8.17)	<b>0.039</b>	-	0.782	-	-	
TLG post-CRT	53.1	0.645	<b>0.029</b>	4.52 (1.60-12.7)	<b>0.004</b>	-	0.58	-	0.702	-	-	
%MTV change >69%*	-	-	0.791	-	0.818	-	-	2.18 (1.00-4.74)	<b>0.045</b>	2.30 (1.36-18.9)	<b>0.034</b>	

pCR: Pathologic Complete Response; ROC: Receiver Operating Characteristic Curve; UVA: Univariate Analysis; MVA: Multivariate Analysis; AUC: Area Under the Curve; OR: Odds Ratio; HR: Hazard Ratio; MTV: Metabolic Tumor Volume; CRT: Concurrent Chemoradiation; TLG: Total Lesion Glycolysis  
 \*%MTV change defined as (pre-CRT MTV – post-CRT MTV)/(pre CRT MTV) × 100

**Table 2:** Receiver operating characteristic, univariate and multivariate analysis.

to esophagectomy. MTVs were defined based on an absolute threshold of SUV 2.5 (MTV2.5) or relative threshold of 20% of SUVmax (MTV20%). Both MTV values correlated with OS on UVA while SUVmax did not. Chang and Kim [21] found MTV to be the most potent predictor of OS in 44 patients. In a larger study of 90 patients with SCC of the esophagus treated with definitive CRT using the same threshold values of SUV 2.5 and 20% of SUVmax, only MTV 20% was found to correlate with DFS and OS on UVA [17]. Hyun et al. [15] found MTV to correlate with OS on MVA in 151 patients treated with a variety of treatment modalities including esophagectomy alone or followed by adjuvant chemotherapy and/ or radiation therapy, definitive CRT, or palliative therapies. They used a unique method for calculating MTV based on a pilot study that determined the ideal SUV threshold based on pathological tumor size of surgical specimens. They found that the ideal threshold was inversely correlated with a dynamic percentage of SUVmax. They then adopted the average value of the optimal threshold within each first, second, third, and fourth quartile stratified by SUVmax. The threshold values used were 3.5 for tumors with SUVmax <10, 5.0 for tumors with SUVmax between 10 and 20, and 6.5 for tumors with SUVmax >20. MTV was found to be an independent prognostic factor for OS and a better predictor of survival than SUVmax. Finally, Lemarignier et al. [16] evaluated 67 patients with SCC treated with definitive CRT. They chose an SUV threshold to best fit the MTV volume to the physician delineated gross tumor volume (primary tumor and lymph nodes) based on visual inspection. They found that pre CRT MTV correlated to DFS and OS on MVA. They found no correlation between TLG and survival. Conversely, Hong et al. [27] found TLG to be the best predictor of OS in 38 patients using an absolute threshold of SUV 2.5 (MTV2.5) to define the MTV. These studies evaluated pre CRT PET/CT parameters and survival. They did not evaluate post CRT PET/CT scans or pathologic response.

Two studies [19,20] have compared pre CRT PET/CT parameters to pathologic response determined by biopsy. Hatt et al. [19] found that pre CRT MTV, TLG and tumor length (TL) predicted for OS and pathologic response as determined by biopsy in 50 patients treated with definitive CRT. They used two methods for delineating their volume of interest: Fuzzy Local Adaptive Bayesian (FLAB) algorithm (an automatic software program) and an adaptive threshold algorithm based on a manually defined background VOI defined by two nuclear medicine physicians. A prospective trial has evaluated the correlation of PET/CT parameters pre CRT and at day 21 of CRT with response as determined by clinical exam, CT, PET/CT and biopsy in 48 patients with SCC of the esophagus treated with definitive CRT [28]. They found that high baseline MTV and TLG were predictive of response at 3 months and 1 year and that SUVmax was predictive of response at 1 year. PET/CT at day 21 of CRT appeared less clinically relevant

although high MTV at day 21 was predictive of poor clinical outcome. To determine the volume of interest from which to extract PET/CT parameters, this study used a relative threshold of 40% and physician delineated volumes.

Ours is not the first study to correlate MTV and TLG pre and post CRT to pathologic response as determined from surgical specimens. Arslan et al. [24] evaluated MTV, SUVpeak, SUVmean and TLG between pre CRT and Post CRT scans in 24 patients with esophageal cancer, 20 of whom underwent esophagectomy. They used absolute (SUV 2.5) and relative (50% of SUVmax) threshold methods for contouring their VOI from which they obtained MTV and TLG values. They found that only change in MTV identified patients who underwent a pCR. Jayachandran et al. [23] evaluated 37 patients with esophageal cancer treated with either neoadjuvant (21) or definitive (16) CRT. They evaluated MTV and TLG values calculated using absolute (SUV 2.0, 2.5 and 3.0) and relative (50% of SUVmax) threshold methods, as well as MTV ratio values defined as pre CRT MTV/ post CRT MTV for each SUV threshold. They found no correlation between pre CRT parameters and TRG or OS. Post CRT MTV2.5 and TLG2.5 had the greatest correlation with both TRG and OS. The MTV2.0 ratio also correlated with OS. Both these studies were relatively small with heterogeneous treatment modalities including patients treated with definitive CRT and neoadjuvant CRT followed by esophagectomy. In a larger and more homogenous study of 51 patients with adenocarcinoma of the esophagus, treated with neoadjuvant CRT and esophagectomy, utilizing an absolute threshold (SUV 2.5) method, Roedl et al. [25] found that change in TLG was the best predictor of pathologic response with an OR of 12.1 (95%CI 2.7-34.2, p<0.001). They also found that change in MTV was the best predictor for DFS and OS. Finally, a small prospective trial of 31 patients found no PET parameters (before, during or post CRT) to be predictive of pCR [29]. TLG, however, was predictive of OS.

This body of literature supports the superiority of MTV and/or TLG over SUV values to predict pathologic response and survival in patients with LAEC treated with either neoadjuvant or definitive CRT. However, the method of calculating MTV and TLG varies widely among these studies. Furthermore, there is significant discrepancy between which MTV and TLG values (pre CRT, post CRT or change) are the best predictors of response and survival. This can be attributed to the variety of methods used to calculate MTV and TLG, the heterogeneous tumor histologies (SCC and ACC), the heterogeneous treatment modalities (definitive CRT and neoadjuvant CRT followed by esophagectomy), and the varying definitions of response (biopsy and surgical specimens). Finally, the prognostic value of imaging biomarkers and tumor heterogeneity is currently underway and has the potential to improve prediction accuracy even further. A prospective trial utilizing a standardized, reproducible method for delineating a

VOI that accounts for individual patient background FDG uptake from which PET/CT parameters can be extracted is warranted to establish the ideal PET/CT parameters to predict for pathologic response and survival. Patients should also be stratified by histology and treatment modality.

A recent study randomized patients with LAEC who had a non-complete metabolic response to definitive CRT determined by SUV uptake at completion of 50.4 Gy to either no further radiation or radiation dose escalation [34]. They found an improvement in local control and overall survival with dose escalation. Given that MTV and TLG have been shown to be better determinants of response and survival than SUV, perhaps a similar prospective trial is warranted utilizing MTV and TLG to determine complete versus non complete metabolic response. This could allow radiation oncologists to more confidently adapt radiation dose based on metabolic response and could potentially guide recommendations for esophagectomy.

## Conclusions

Pre CRT MTV, pre CRT TLG and post CRT TLG are predictive of pCR and percent change in MTV is predictive of OS. Our data suggests that MTV and TLG are superior to SUVmax and SUVpeak in predicting pathologic response and survival in LAEC. Current investigation is underway to assess whether tumor heterogeneity and imaging biomarkers can further improve prediction accuracy. Prospective studies are needed to determine the ideal imaging parameters to help define which patients will most benefit from radiation dose escalation and esophagectomy.

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