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Prognostic Value of F-18 FDG PET/CT Volume-Based Metabolic Parameters in Patients with Cancer Esophagus.

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ABSTRACT:

Aim: To evaluate the prognostic value of the initial quantitative PET/CT parameters in terms of therapy response and survival in patients with esophageal carcinoma. **Material &methods:** This retrospective study includes thirty-two patients (17 males and 15 females). All patients had pathologically proven esophageal cancer. These Patients underwent whole body 18F-FDG PET/CT as a baseline staging method before Neoadjuvant therapy. Initial FDG PET/CT scans were retrieved and PET volumetric images were analysed for metabolic parameters including maximum SUV (SUV max), mean SUV (SUV mean), (SUV peak), MTV and TLG. **Results:** 53.1% of the enrolled patients were males and 46.9%were female with the dominating pathological subtype was Squamous cell carcinoma in 20 patients (62.5%). Quantitative analyses of the metabolic parameters of the enrolled patients revealed SUV max with average value 16.13 +/- 8.71, SUV mean with average value 9.47+/- 5.2, SUV peak with average value 13.09 +/-7.1. MTV with average value 32.5+/-21.88 and TLG with average value 332.44+/- 318 and range between (34 and 1149)**.** Survival analysis showed that initial SUV max, SUV mean, SUV Peak of oesophageal tumour were not correlated with OS. While MTV and TLG were correlated with OS with p value of 0.045 and 0.031 respectively.

Conclusion: The initial PET/CT MTV and TLG metabolic parameters are prognostic parameter for response and survival is more efficient than the other metabolic parameters in patients with esophageal cancer.

Key Words.: 18F-FDG PET/CT & Metabolic Parameters& SUV & MTV and TLG.

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INTRODUCTION:

Esophageal cancer [EC] is the sixth most common cause of cancer deaths worldwide. Incidence rates vary within different geographic locations with Squamous cell carcinoma being the most common subtype and it is the fourth most common cause of cancer deaths in third world countries [1, 2]. According to National Cancer Institute, Egypt published in 2016 that esophageal cancer represents 6-8% of all malignancies in Egypt with affected patients have a mean age of 58.7 years and the male to female ratio is 1.9.

F18-FDG PET/CT has become the standard imaging modality in patients with different malignant lesions. It has been shown that its significant in evaluation of esophageal cancer (EC) in detection of distant metastases compared to CT alone [1,2].

The prognostic values of metabolic parameters measured by 18F-FDG PET/CT remain to be determined. Maximum SUV [SUV max] is a widely accepted functional biomarker derived from 18F-FDG PET/CT for several types of malignancies [3]. However, SUV max is highly dependent on the statistical quality of the images and the size of the maximal pixel also a lot of tumours are irregular and non-homogenous in nature rendering SUV parameters to be inaccurate [4]. The concept of volumetric parameters has emerged that have the potential to better mirror the true tumour biology with the use of both the metabolic tumour volume [MTV] as well as total lesion glycolysis [TLG] that reflect FDG avidity of the entire tumour is displayed in prediction of prognosis and survival.

Li et al (2019) in a large retrospective study with results showing the positive predictive value of initial MTV and TLG [(5)]. While **Jayachandran et al (2012)** showed no correlation between PET/CT metabolic parameters and response [(6)]. So, such difference in the role of metabolic parameters leads us to try and establish our aim in evaluation of prognostic role of such parameters in EC in Egyptian population.

PATINTS AND METHODS:

This retrospective study was conducted in national cancer institute during the period from January 2015 to December 2019. The study included thirty-two patients (17 males and 15 females). All patients had pathologically proven esophageal cancer. These Patients underwent whole body 18F-FDG PET/CT as a baseline staging method before Neoadjuvant therapy.

PET/CT imaging protocol:

Patients asked to fast for 6 hours before the F18-FDG PET/CT. Blood glucose levels of all patients were less than 160 mg/dl at the time of the scan. Patients were injected with 3-7 MBq/Kg of 18F FDG. During the uptake phase of the FDG, patients were kept in a quiet warm room. Fifty to sixty minutes after IV injection of 18F FDG, the patients were examined in the supine position with arms elevated, and CT scanning was started at the level of skull base with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during shallow normal breathing and reached caudally to the mid thighs. PET over the same region was performed immediately after acquisition of the low dose CT images. CT-data were used for attenuation correction, and images were reconstructed as 3-mm slices applying a standard iterative algorithm. Images were interpreted at a workstation equipped with fusion software that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Image interpretation was accomplished by experienced two nuclear medicine physicians.

Image interpretation

[A] Qualitative assessment:

An abnormal focus of FDG uptake is visually identified according to site and number of lesions.

[B] Quantitative assessment:

The intensity of FDG uptake within specific lesion is calculated by using volumetric region of interest (ROI) over the lesion then the following parameters were calculated:

1) SUV max was generated according to the following formula:

$$\textbf{SUV max} = \frac{\text{ROI activity (mCi /mL) x body weight (gm)}}{\text{Injected dose (mCi)}}$$

2) SUV mean = (SUV-bw).

3) SUV peak = (SUV-bw/size: 1 cm^3).

- **TMTV metabolic tumor volume:** voxels with **40 %** or more of the SUV max of the lesion are incorporated to define the volume of each individual lesion

4) **Total Lesion Glycolysis (TLG)** = mean SUV x metabolic tumour volume.

Evaluation of clinical response and survival: Personnel clinical follow up data were collected for each individual patient to establish the clinical response of every patient.

Complete response; Negative CT in addition to negative endoscopic biopsy or negative PET/CT.

Partial response; decrease more than 30% in SUV on PET/CT**.**

Progressive disease; progression of the esophageal lesion, new loco-regional or distant lesions.

Stable disease; decrease less than 30% in SUV of primary lesion with no appearance of new lesions or metastatic lesions on PET/CT or CT.

Follow up survival data has been retrieved and correlated with initial PET/CT findings.

[C] Statistical analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests ***(Chan, 2003a)***. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 ***(Chan, 2003b)***. ROC curve was constructed with area under curve analysis performed to detect best cut-off value of different parameters for detection of response. P-values less than 0.05 were considered as statistically significant.

RESULTS:

Thirty-two patients with newly diagnosed esophageal cancer were referred for initial PET/CT study in our department. Out of these 32 patients, 17 were males (53.1%) and 15 females (46.9%).

Their mean age was 58.34 +/- 10.46 with range between (35 and 75 years)**.**

Most of the Oesophageal lesions were SCC in 20 patients (62.5%), 7 patients were adenocarcinoma (21.9%) while 5 patients (15.6 %) were poorly differentiated. Most of them were located at gastro-oesophageal junction in 12 patients (37.5%), 7 patients (21.9%) were at distal part, 4 patients (12.5%) at mid and 9 patients (28.1%) at proximal part.

All patients received adjuvant chemo/radiotherapy with the dose of radiotherapy ranging between 2000 and 5400 cGy.

Metabolic parameters of initial PET/CT of patient's population:

Initial FDG PET/CT scans were retrieved and PET volumetric images were analysed for metabolic parameters including maximum SUV (SUV max), mean SUV (SUV mean), (SUV peak), MTV and TLG.

The patients showed SUV max with average 16.13 +/- 8.71, SUV mean with average 9.47+/- 5.2, SUV peak with average13.09 +/-7.1. MTV with average 32.5+/-21.88 and TLG with average 332.44+/- 318 with range between (34 and 1149) ***(Table 1).***

Table (1): Different metabolic parameters in 32 patients with oesophageal cancer.

	Mean	Standard Deviation	Median	Minimum	Maximum
SUV max	**16.13**	**8.71**	**13.50**	**6.00**	**42.00**
SUV mean	**9.47**	**5.20**	**8.00**	**3.00**	**27.00**
SUV peak	**13.09**	**7.10**	**11.50**	**4.00**	**37.00**
TMTV	**32.50**	**21.88**	**25.00**	**2.00**	**79.00**
TLG	**332.44**	**318.04**	**204.00**	**34.00**	**1149.00**

Additive value of PET/CT

The baseline PET/CT done for these patients was able to detect more lesions than CT in 12 patients (37.5%) that caused upstaging of disease in 7 patients (21.9%) ***(Table 2).***

The lesions added by the PET/CT were found at cervical LNs in five patients, mediastinal LNs in two patients, para aortic LNs in two patients, bone lesions in two patients and liver lesion in one patient.

The nodal lesions were small sub-centimetric and centimetric, so the diagnostic CT was not able to verify them as pathological nodes, however they showed abnormal increased FDG activity in PET, the bone lesions were bone marrow based with no corresponding CT changes and the hepatic focal lesion was not seen at the diagnostic CT as it was without contrast, however in the PET/CT, the lesion was intensely FDG avid.

Table (2): Value of PET/CT in detection of more lesions and in upstaging staging of Oesophageal cancer**.**

	No. Of patients	%
More lesions detected by PET/CT	12	37.5%
Up Staging	7	21.9%

In this study, 20 patients showed loco regional metastases, these lesions were found in the regional LNs, six patients with cervical LNs, four patients with mediastinal LNs, one patient with supra-clavicular LN and nine patients with coeliac and peri- gastric LNs. They showed average SUV max of 10.6. While 10 patients had distant metastases that were found at distant nodes, lung, liver and bone with average SUV max of 11.2.

Out of the 32 patients, 8 patients were responder with good (complete and partial response) to treatment and 24 patients were non responders (stable and progressive) disease. Twenty patients died during the follow up period (with range between 2 months and 23 months) because of the tumour and 12 patients were still alive by the end of the study.

Overall survival of oesophageal cancer patients in this study is 13.16+/- 11.48 months.

Survival analysis showed that initial SUV max, SUV mean, SUV Peak of oesophageal tumour were not correlated with OS. While MTV and TLG were correlated with OS with p value of 0.045 and 0.031 respectively ***(Table 3).***

Table (3) Correlation between survival and metabolic parameters of initial PET/CT of 32 patients with oesophageal cancer.

Parameters	Correlation Coefficient	P Value
SUV max	-0.222-	0.222
SUV mean	-0.147-	0.423
SUV peak	-0.181-	0.321
TMTV	-0.357-	0.045
TLG	-0.382-	0.031

Correlation of metabolic parameters of initial PET/CT and clinical response:

Clinical response assessment was done post treatment then Univariate response analysis showed only TLG had border line significant value to be predictive of response. TLG (with mean 147+/- 118) of initial PET/CT was predictive of clinical response. (p=0.05) ***(Table 4)***.

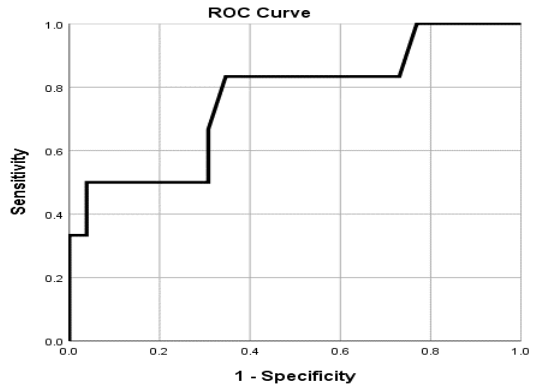
Table(4): Correlation between response and metabolic parameters of initial PET/CT.

	responders					Non Responder					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
SUV max	14.50	10.43	10.00	7.00	36.00	16.67	8.24	15.50	6.00	42.00	0.188
SUV mean)	8.63	5.80	6.50	4.00	20.00	9.75	5.08	9.00	3.00	27.00	0.334
SUV peak	11.25	6.84	8.50	6.00	23.00	13.71	7.21	12.00	4.00	37.00	0.237
TMTV	22.00	18.51	17.50	2.00	50.00	36.00	22.13	30.00	8.00	79.00	0.086
TLG	147.13	118.36	115.50	34.00	373.00	394.21	340.80	215.00	35.00	1149.00	0.051

ROC curve analysis was performed to assess the AUC and determine the optimal cut-off values for predicting good responders. Lower MTV prior to CRT predicted good responders at an optimal cut-off of 23 with a sensitivity of 83% and a specificity of 65% (AUC of 0.763, p=0.048). Pre CRT TLG also predicted good responders, at an optimal cut-off of 82 with a sensitivity of 66 % and specificity of 92.3% (AUC 0.821, p=0.05). Whereas other metabolic parameters showed no predictive value **(Table 5 and Fig 1a and b).**

Table (5): Metabolic parameter's correlation with Response ROC curve/

	Area Under the Curve	P value	95% Confidence Interval		Cut off	Sensitivity %	Specificity %
			Lower Bound	Upper Bound			
SUV max (Local)	0.686	0.161	0.421	0.950	---	---	---
SUV mean (SUV-bw) (Local)	0.638	0.299	0.373	0.903	---	---	---
SUV peak (SUV-bw/size: 1 cm3) (Local)	0.673	0.192	0.417	0.929	---	---	---
TMTV (Local)	0.763	0.048	0.531	0.994	23	83.3	65.4
TLG (Local)	0.821	0.016	0.626	1.000	82	66.7	92.3



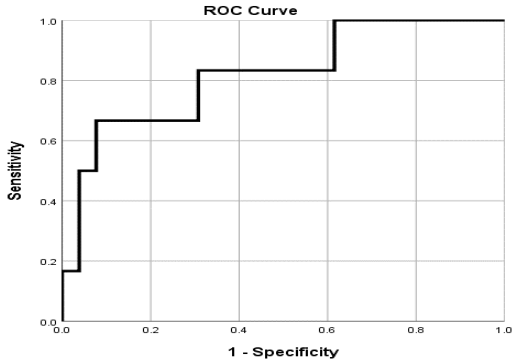
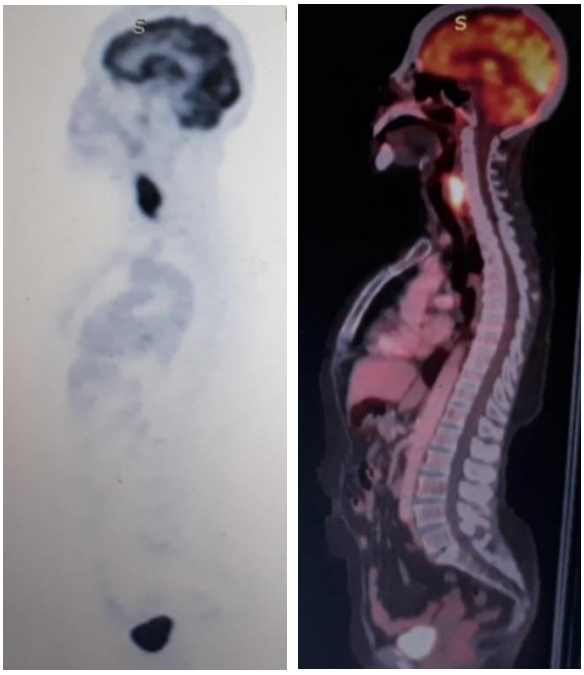


Figure 1 A: ROC curve for detection of complete response using TMTV in Oesophageal cancer

Figure 1 B: ROC curve for detection of complete response using TLG in Oesophageal cancer.



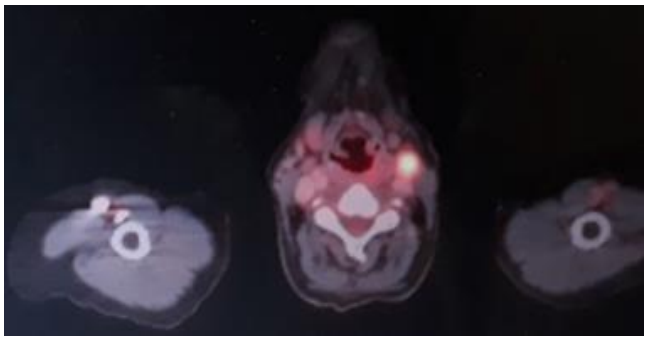


Fig (3): 66 yrs. old female patient with SCC in cervical oesophagus with cervical LNs leading to upstaging of the disease. She had high metabolic parameters including MTV; TLG predicted the bad response associated with disease progression of loco-regional disease within 6 months after therapy.

DISCUSSION:

Endoscopy is the main method of diagnosis of esophageal cancer. PET/CT as metabolic imaging is involved in the initial staging of many malignant tumours with possible change in the stage of the disease which is reflected on treatment plan, the value of metabolic parameters to predict survival and possible outcome should be determined [(3)].

SUV max has been widely used in evaluation of treatment response, However, it may have some limitations which lead the direction of most recent studies to focus on metabolic volumetric parameters that have the potential to reflect the true tumour biology. The metabolic tumour volume [MTV] and total lesion glycolysis [TLG] are useful being reflecting FDG avidity of the entire tumour [(4, 7)].

In this retrospective study population, the initial PET/CT in 32 patients with pathologically proven esophageal cancer was correlated with short term clinical response and survival to establish the significance of their relationship.

The main strength of FDG-PET/CT in esophageal cancer is in evaluating distant metastases, unexpected metastases are present are found in 20–30 % of esophageal tumours at initial staging.

It has been shown to improve preoperative staging and prevent inappropriate intervention, and even in patients not suitable for surgery. The most common sites for metastatic disease are non-regional nodes. However, PET/CT also has a high sensitivity for detecting distant metastases [(8)].

In the present study the initial PET/CT showed new lesions in 12 patients out of 32 (37.5%) causing upstaging of the disease in 7 out of 12 patients (21.9%).

In agreement to our results, Also, **Tan et al (2016)** reported in a retrospective study of 40 patients done. PET/CT lead to change in staging in 23 patients (65 %) leading to change in management plans in 17 of them [(9)].

Furthermore; in a retrospective study involving 45 patients done to assess the prognostic power of different PET/CT metabolic parameters, **Hatt et al (2011)** found that pretreatment SUV measurements were not significant prognostic factors for overall survival while metabolic tumor volume (MTV) and tumor length (TL) TV ($p < 0.002$) and TL ($p = 0.042$) predicted for OS treated with definitive chemo/radiotherapy [(10)].

Similarly, in a large retrospective study of 86 patients which was done to evaluate if Pre-treatment metabolic parameters of esophageal squamous cell cancer patients are useful prognostic factors. The study included 86 patients with ESC with different stages prospectively enrolled.

18F-FDG PET/CT scans were performed before the treatment. SUV max, MTV, and TLG were measured. Results of the study showed that MTV and TLG proved to be good indexes in predicting outcome for the esophageal cancer patients.

An MTV value of 15.6 ml and a TLG value of 183.5 were optimal threshold to predict the overall survival (OS). The areas under the curve (AUC) for MTV and TLG were 0.74 and 0.70, respectively. Kaplan-Meier analysis showed an MTV less than 15.6 ml and a TLG less than 183.5 to indicate good media survival time (p value <0.05). In the stage III-IV patient group, MTV could better predict the OS (P < 0.001), with a sensitivity and specificity of 0.80 and 0.67, respectively while SUV max, site, age and gender showed no correlation [(11)].

In the present study, as we found significant relationship between MTV and TLG with overall survival and clinical response while no association between them and other metabolic parameters including SUV max, mean and peak. Our results showed an overall survival of our patient's population with mean 13.16 months +/-11.48, no significant relationship was found between SUV max, mean and peak and overall survival but a correlation was found between MTV and TLG and overall survival with p value 0.045 and 0.03 respectively. Also our results found a relationship between response and TLG with p value 0.05.

Also ROC analysis of the relationship between metabolic parameters and response showed that only MTV and TLG were significant with p value 0.048 and 0.016, cut of value 23 and 82 and AUC (area under curve) 0.763, 0.821 respectively.

Consistent with our results, **Hong et al 2015** in a retrospective study involving 38 esophageal cancer patients done to assess the prognostic power of initial TLG in these patients. Results showed that TLG has higher sensitivity and specificity for predicting OS than SUV P=0.003) [(12)].

Also in **Venkat et al 2016,** another large retrospective study involving 76 patients about the prognostic value of PET/CT metabolic tumour volume in relation to

Pathologic response and clinical outcomes after therapy in esophageal cancer patients, results of this study were similar to ours showing that Pre CRT MTV and pre CRT TLG were independently predictive of response (MTV ; cut off = 33,1 and p = 0.004 while TLG; cut of=153 and p=0.007, and percentage change in MTV independently predicted for overall survival [(13)].

Moreover, **Li et al** (2019) a large retrospective analysis involving 134 patients about the predictive value of metabolic parameters of sequential PET/CT studies in esophageal cancer patients in relation to overall survival, in their study all metabolic parameters were correlated individually with OS (initial SUV max, post therapy SUV max and their % change, initial MTV, post therapy MTV and their %change, initial TLG, post therapy TLG and its %change). Results showed no significant relationship between stage of the disease, SUV max (initial, post therapy and% change) with survival but it did show positive predictive value for initial MTV and TLG agreeing with our results and also it did show significant relationship with both their % change [(5)].

On the other hand, **Elimova et al, (2015)** a small prospective trial of 31 patients found no PET parameters (before, during or post CRT) to be predictive of pathological response. TLG, however, was predictive of OS. There was association between OS and baseline TLG (p=0.03) at the optimal cutoff TLG value of 75.15 [(14)].

On the contrary, ***Jayachandran et al***, evaluated 37 patients with esophageal cancer. They found no correlation between pre CRT parameters and TRG (tumor regression grade) or OS. Only post treatment parameters showed significance; Post CRT MTV2.5 and TLG2.5 had the greatest correlation with both TRG and OS [(6)].

An accurate prediction of pathologic responses is critical, since patients with poor responses are exposed to unnecessary treatment-related toxicities, Therefore, the predictive value of 18F-FDG PET/CT response during treatment has been widely accepted in preoperative chemotherapy for patients with esophageal cancer as well as the baseline 18F-FDG PET/CT [(15,16)].

Study limitations: Small sample sizes, different histopathological types are included in this study and no standard protocol is used in evaluation of esophageal cancer in this retrospective study.

CONCLUSIONS: the results of this study in association with the majority of the similar studies in the same area supports the superiority of MTV and TLG over other metabolic parameters in patients with esophageal cancer as a prognostic parameter for response and survival.

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