

Prognostic Value of Quantitative 18F-FDG PET/CT Parameters Measured in Primary Tumors and Suspicious Lymph Nodes in Patients With Esophageal Carcinoma

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Research article

Keywords: Esophageal neoplasms, Neoadjuvant therapy, PositronEmission Tomography, Nuclear Medicine

Posted Date: June 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-32577/v1>

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Abstract

Objective:

Quantitative ^{18}F -FDG PET/CT parameters have been described as prognostic indicators in esophageal cancer. The objective of this study is to evaluate the prognostic value of the maximum standardized uptake value (SUVmax), metabolic tumor value (MTV) and total lesion glycolysis (TLG) measured in the primary tumor and suspicious lymph nodes.

Methods:

A cohort study was performed to assess the association of SUVmax, MTV and TLG measured prior to and post neoadjuvant therapy with overall survival (OS) of patients with esophageal cancer who received trimodal therapy. The quantitative techniques were applied in the primary tumor and suspicious lymph nodes. The OS rates were analyzed.

Results:

Before neoadjuvant therapy, 106 patients underwent PET/CT, and 39 patients underwent post-neoadjuvant therapy PET/CT exams. Before neoadjuvant therapy, PET/CT showed that all the variables of the evaluated lymph nodes were statistically significant in predicting OS. Postneoadjuvant therapy, none of the PET/CT variables of lymph nodes were related to prognosis. On the other hand, all primary tumor volumetric variables were related to overall survival. The MTV (HR: 4.66; 95% CI: 1.54-14.08) and TLG (HR: 4.86; 95% CI: 1.66-14.26) of the primary tumor post neoadjuvant therapy and the variations in MTV (HR: 2.95; 95% CI: 1.01-3.52) and TLG (HR: 3.49; 95% CI: 1.01-3.52) of the primary tumor pre-to-post-neoadjuvant therapy were prognostic variables.

Conclusion:

In patients with esophageal cancer, the burden of disease in suspicious lymph nodes and the primary tumor prior to therapy and the residual burden of disease in the primary tumor post therapy assessed by PET/CT were associated with prognosis.

1. Introduction

Since the CROSS group ¹ reported good results after neoadjuvant therapy based on carboplatin and paclitaxel, preoperative chemoradiotherapy has become the mainstay treatment among most patients with potentially curable esophageal cancer. ^{1,2} On the other hand, patients with poor response to neoadjuvant therapy present poor long-term survival rates and might not be the best candidates for surgical resection. ³ To reach the correct treatment decisions and to reduce therapeutic toxicity, the selection of patients who have favorable prognoses plays an important role.

^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) provides the ability to functionally evaluate metabolic activity ^{4,5}, thus improving patient selection for surgical treatment. ⁶

The pretreatment standardized uptake value (SUV) is the most widely used parameter in ^{18}F -FDG PET/CT and is considered a prognostic factor for risk stratification; however, this parameter does not reflect the heterogeneity of the primary tumor or lymph nodes. ⁷ Aggressive tumors grow rapidly and usually present intratumoral hypoxia ⁷ and necrosis, which leads to heterogeneous FDG accumulation in the tumor. ^{8,9} In this context, volume-based parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) that reflect metabolic volume and activity in an entire mass, respectively, have been proposed as quantitative indexes of tumor metabolism. MTV is a volumetric measure of the tumor cells with high glycolytic activity, while TLG is defined as the product of the tumor volume by the average SUV inside this volume. ¹⁰ These indexes are prognostic indicators for survival in several neoplasms, such as lung cancer, pleural mesothelioma, ovarian cancer, and head and neck cancer. ¹¹⁻¹⁸

There have been a few studies on the prognostic value of MTV and TLG for esophageal cancer treated with trimodal therapy. ¹⁹⁻²⁶ Nonetheless, these studies included heterogeneous neoadjuvant therapy regimens and did not present separate analyses of primary tumors and lymph nodes.

Therefore, the aim of this study is to assess the value of the maximum SUV (SUVmax), MTV and TLG of the primary tumor and suspicious lymph nodes, as measured with ^{18}F -FDG PET/CT prior to and post therapy, in predicting overall survival in a group of patients with esophageal cancer treated with neoadjuvant chemoradiotherapy using a platinum- and taxane-based regimen followed by curative intent esophagectomy.

2. Methods

A retrospective cohort study was performed in a group of patients with esophageal cancer, assessing the association of SUVmax and volumetric parameters (MTV and TLG) measured on ^{18}F -FDG PET/CT studies performed prior and post neoadjuvant therapy, as well as the variations in these values pre-to-post neoadjuvant therapy, with overall survival (OS). The ^{18}F -FDG PET/CT parameters of both the primary tumor and lymph nodes were estimated (see Fig. 1).

2.1 Patients

The patients originated from a single institute and completed neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens, followed by curative intent esophagectomy. A transthoracic approach with two-field lymph node dissection was performed for tumors extending proximally to the tracheal bifurcation. For tumors involving the esophagogastric junction, a transhiatal resection was preferred. Gastric tube reconstruction with cervical anastomosis was the preferred technique.

The recruitment period ranged from 2009 to 2019. Patients were staged with endoscopy, CT, and PET and classified according to the 8th edition of the UICC staging system²⁷. The local ethics committee approved the study.

2.2 ¹⁸F-FDG PET/CT acquisition and imaging analyses

¹⁸F-FDG PET/CT scans were acquired on a Discovery 690 with time-of-flight (General Electric, Waukesha, Wisconsin, USA). The patients were injected with ~3.7 MBq ¹⁸F-FDG per kg body weight. The patients were instructed to fast for at least 6 h and had a blood glucose level below 180 mg/dl before the radiopharmaceutical injection. Imaging was initiated 60 min after the injection, and the scans were acquired from the mid-skull to mid-thigh. The images were reconstructed with a standard iterative algorithm, and the burden of disease in the primary tumor and metastatic lymph nodes were evaluated using SUVmax, TLG and MTV. These variables were calculated by a nuclear medicine physician using AW VolumeShare 5® (General Electric, Waukesha, Wisconsin, USA). The SUV thresholds used to define the boundaries of the lesions were established by visual analysis, and the total volumes of interest that circumscribed the primary tumor and metastases were calculated automatically by the software.

The burden of the disease was measured on ¹⁸F-FDG PET/CT scans acquired prior to and post neoadjuvant therapy.

2.3 Statistical analyses

Survival analysis was performed with Kaplan-Meier and log-rank tests. For long-term survival analysis, all patients who died within 30 days postoperatively were excluded from the analysis, and the cutoff was defined as the threshold value of the continuous covariate determined by Lausen.²⁸ A significance level of 0.05 was adopted. Cox proportional hazard analysis was performed. In the multivariate analysis, the ¹⁸F-FDG PET/CT parameters, age, sex, clinical stage, and grade of cellular differentiation were assessed.

3. Results

3.1 Patients' baseline characteristics

One hundred seventeen patients underwent neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens followed by curative intent esophagectomy and were included. Of these patients, 8 patients who died within 30 days postoperatively were excluded. One hundred and six patients underwent PET/CT before neoadjuvant therapy, and 39 of these patients also had post-neoadjuvant therapy PET/CT exams. Squamous cell carcinoma (SCC) comprised 70% of the cases, and adenocarcinoma comprised the remaining cases. The mean follow-up was 36.8 months (SD ± 24.9), with a mean age of 60.9 years (SD ± 8.2), and there was a male predominance (78.9%). There were 87 transthoracic (video-assisted thoracoscopic) procedures and 22 transhiatal procedures, all of which involved cervical anastomosis. The median time from the completion of neoadjuvant chemoradiotherapy to surgery was 13.4 (± 6) weeks. The two chemotherapy regimens adopted were carboplatin and paclitaxel (78%) and cisplatin and paclitaxel (22%). The radiation therapy dosages were 41.4 cGy (75.3%), 45 cGy (12.8%), and 50.4 cGy (11.9%). See Table 1.

Table 1
Patients' baseline characteristics. CRT: Chemoradiotherapy.

N	Pre neoadjuvant therapy PET	106	
	Post neoadjuvant therapy PET	39	
Age (years; mean ± SD)		60.9	8.2
Sex (n, %)	Male	86	78.9
	Female	23	21.1
Histology (n, %)	Adenocarcinoma	32	29.4
	SCC	77	70.6
Clinical stage (n, %)	I/II	33	30.3
	III/IV	76	69.7
Grade of cellular differentiation (n, %)	I	8	7.3
	II	75	68.9
	III	26	23.8
Radiation therapy (n, %)	41.4	82	75.3
	45	14	12.8
	50.4	13	11.9
Chemotherapy regimen (n, %)	Cisplatin/paclitaxel	24	22
	Carboplatin/paclitaxel	85	78
Time interval between CRT and surgery (weeks; median ± IQR)		13.4	6
Surgical access (n, %)	Transhiatal	22	20.2
	Thoracoscopic	87	78.8
Lymph nodes dissected (mean ± SD)		21.4	12.7
Cervical leakage (n, %)		28	25.7

3.2 Overall survival

Prior to neoadjuvant therapy, ¹⁸F-FDG PET/CT showed that all the variables of the evaluated lymph nodes were statistically significant in predicting long-term survival (See Fig. 2). The MTV of the primary tumor (HR: 1.89; 95% CI: 1.01–3.52; $p = 0.04$) was also able to predict overall survival. See Table 2.

Table 2
The relationship between the ¹⁸F-FDG PET/CT variables and overall survival.

		All cases			Adenocarcinoma					Squamous cell carcinoma						
		Variable	Cut-off point	HR	95% CI		p-value	Cut-off point	HR	95% CI		p-value	Cut-off point	HR	95% CI	
					Lower	Upper				Lower	Upper				Lower	Upper
Pre neoadjuvant therapy	Primary tumor	SUVmax	≥ 21.84	2.42	0.85	6.9	0.09	≥ 22.22	2.4	0.29	19.58	0.43	≥ 5.5	2.23	0.3	
		MTV	≥ 23.76	1.89	1.01	3.52	0.04	≥ 108.68	0.88	0.25	3.06	0.82	≥ 11.46	1.02	0.43	
		TLG	≥ 17	3.5	0.48	25.52	0.19	≥ 647.7	0.59	0.13	2.59	0.46	≥ 17	2.66	0.36	
	Lymph nodes	SUVmax	≥ 2.9	2.28	1.14	4.56	0.02	≥ 7.9	0.57	0.12	2.63	0.47	≥ 2.98	2.91	1.12	
		MTV	≥ 1.55	2.05	1.02	4.1	0.04	≥ 2.31	1.75	0.48	6.43	0.37	≥ 1.55	2.5	0.99	
		TLG	≥ 3.6	2.44	1.28	4.66	0.01	≥ 17.4	1.2	0.26	5.46	0.79	≥ 4.1	2.46	1.03	
Post neoadjuvant therapy	Primary tumor	SUVmax	≥ 8.31	2.82	0.62	12.88	0.16	≥ 4.761	0.22	0.01	3.59	0.25	≥ 5.1	0.74	0.15	
		MTV	≥ 16.23	4.66	1.54	14.08	0	≥ 6.85	NE	NE	NE	NE	≥ 16.23	1.61	0.4	
		TLG	≥ 55.9	4.86	1.66	14.26	0	≥ 20.5	NE	NE	NE	NE	≥ 55.9	1.59	0.33	
	Lymph nodes	SUVmax	≥ 2.9	1.26	0.35	4.53	0.74	≥ 0	NE	NE	NE	NE	≥ 2.76	1.07	0.22	
		MTV	≥ 1.59	1.48	0.33	6.63	0.62	≥ 0	NE	NE	NE	NE	≥ 1.59	4.59	1.12	
		TLG	≥ 5.4	2.23	0.49	10.1	0.29	≥ 0	NE	NE	NE	NE	≥ 5.4	3.83	0.79	
Variation pre-to-post neoadjuvant therapy	Primary tumor	SUVmax	≥ 11.92	2.81	0.98	8.07	0.05	≥ 6.59	0	0	(-)	0.38	≥ 10.49	8.89	1.06	
		MTV	≥ 12.93	2.95	1.01	8.59	0.04	≥ -19.89	NE	NE	NE	1	≥ 12.93	1.7	0.38	
		TLG	≥ 62	3.49	0.96	12.7	0.04	≥ 460.6	1.42	0.13	16.04	0.77	≥ 678	0	0	
	Lymph nodes	SUVmax	≥ -0.72	>30	0	(-)	0.21	≥ 2.45	0	0	(-)	0.45	≥ 0.84	3.48	0.67	
		MTV	≥ 10.89	0.71	0.09	5.48	0.74	≥ 0.18	0	0	(-)	0.45	≥ 1.59	2.73	0.61	
		TLG	≥ -2.9	>30	0	(-)	0.46	≥ 1.5	NE	NE	NE	NE	≥ 4.5	4.79	0.93	

For lymph nodes, none of the post neoadjuvant therapy ¹⁸F-FDG PET/CT variables or the variations pre-to-post neoadjuvant therapy were related to prognosis. On the other hand, all volumetric variables of the primary tumor were related to overall survival (See Fig. 3). The MTV (HR: 4.66; 95% CI: 1.54–14.08; $p=0.00$) and TLG (HR: 4.86; 95% CI: 1.66–14.26; $p=0.00$) of the primary tumor post neoadjuvant therapy and the variations in the MTV (HR: 2.95; 95% CI: 1.01–3.52; $p=0.04$) and TLG (HR: 3.49; 95% CI: 1.01–3.52; $p=0.04$) of the primary tumor pre-to-post-neoadjuvant therapy were prognostic variables. See Table 2.

In the subgroup analysis, none of the variables related to adenocarcinoma were statistically significant. On the other hand, for squamous cell carcinoma (SCC), the SUVmax and TLG of lymph nodes prior to neoadjuvant therapy; MTV of lymph nodes after neoadjuvant therapy; and the variations in the SUVmax of the primary tumor and TLG of lymph nodes were related to survival. See Table 2.

In the logistic regression, only age and the change in MTV value after neoadjuvant therapy were considered independent variables related to OS. See Table 3.

Table 3
Multivariate analysis.

Multivariate analysis							
	Variable	Group	HR	95% CI		P-value	
				Lower	Upper		
	Age		1.11	1.03	1.20	0.01	
Variation pre-to-post t neoadjuvant therapy	Primary tumor	MTV	≥ 12.93	3.13	1.07	9.18	0.04

4. Discussion

The results of this cohort of esophageal cancer patients who underwent neoadjuvant chemoradiotherapy using a platinum- and taxane-based regimen followed by curative intent esophagectomy suggest that the absolute values of and changes in some of the quantitative ¹⁸F-FDG PET/CT variables predict survival. The lymph node parameters pre neoadjuvant therapy and the primary tumor parameters post neoadjuvant therapy are prognostic factors, mainly for SCC.

MTV and TLG are parameters that reflect both tumor volume and metabolic activity. These parameters provide complementary information about disease burden. In this study, the change in metabolic volume after neoadjuvant therapy and age were unique independent variables related to survival. Although the SUV parameters were related to OS in the univariate analysis, they were not considered independent variables in the final model. SUVmax and SUVmean are semiquantitative indexes that might fail to reflect the spatial distribution of lesions and could vary with different PET scanners, fasting duration, level of plasma glucose and region of interest (ROI). TLG, which is dependent on SUVmean, may also be influenced.

A few studies have assessed SUVmax as a prognostic factor for survival.^{21,29} In addition, several recent studies revealed that the pretreatment MTV and TLG have prognostic value in the prediction of survival in surgically resected or inoperable esophageal cancer.^{19–26} However, these studies used heterogeneous neoadjuvant regimens or surgical approaches, and none of them evaluated metabolic volumetric changes in the lymph nodes. Additionally, these studies used different cut-off points for the logistic regression for survival analysis. The present study used the Lausen cut-off point, which is more suitable for survival analysis when patients are followed for different intervals.²⁸

The results of this study should be interpreted in the context of certain inherent limitations. This is a single-center retrospective study with a relatively small sample size and is mainly focused the period after neoadjuvant therapy. Larger and controlled prospective studies are warranted to clarify the predictive value of these ¹⁸F-FDG PET/CT variables on prognosis.

Despite these limitations, this is the first study to assess the relationship between changes in ¹⁸F-FDG PET/CT variables and survival during neoadjuvant chemoradiotherapy with a platinum- and taxane-based regimen followed by curative intent esophagectomy to treat cancer.

5. Conclusion

PET/CT is a noninvasive imaging method that functionally evaluates metabolic activity, and the absolute values of and changes in SUVmax and volumetric variables provide important information on patient prognosis and may improve patient selection for surgical treatment. Measuring metabolic parameters offers an easy approach towards determining patient prognosis, as the majority of patients receive PET/CT during staging. Clinicians can predict which patients will respond favorably to neoadjuvant therapy and esophagectomy and customize the follow-up of each patient. Personalized medicine is a goal of modern cancer therapy and aims for individually optimized treatments that are dependent on the tumor characteristics of each individual patient.

Declarations

Ethics approval and consent to participate

Local Ethics committee (CCEP) approved this study.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding for this work.

Authors' contributions

- FT: Acquisition of the data.
- FRT: Acquisition, analysis and interpretation of the data.
- PD: Acquisition of the data.
- DA: Revising critically the work.
- CB: Revising critically the work.
- URJ: Statistical analysis and interpretation of the data
- RAAS: Drafting of the study.
- IC: Drafting and supervision of the study.

Acknowledgements

Not applicable.

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Figures

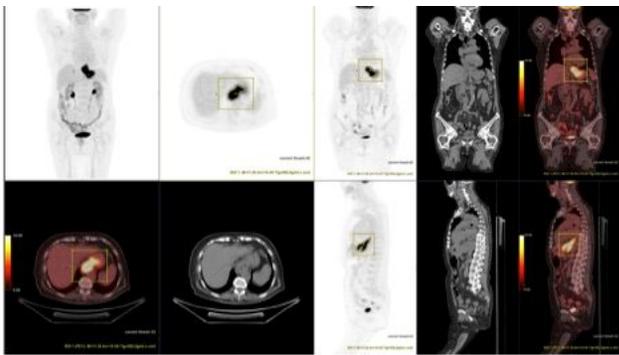


Figure 1

18F-FDG PET/CT. The parameters of both the primary tumor and lymph nodes were estimated.

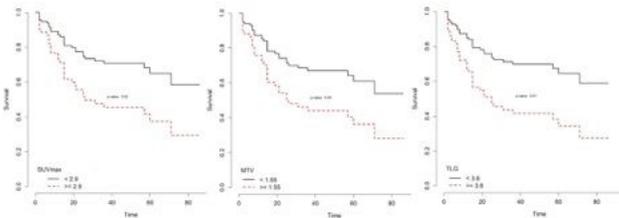


Figure 2

Overall survival according to the 18F-FDG PET/CT parameters of lymph nodes prior to neoadjuvant therapy. Cut-off points were determined by Lausen.

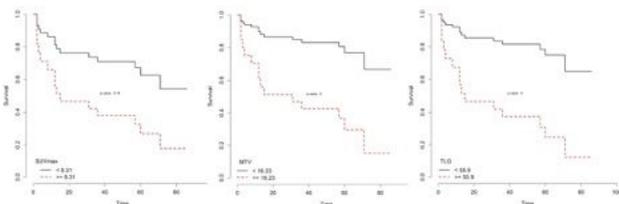


Figure 3

Overall survival according to the 18F-FDG PET/CT parameters of the primary tumor post neoadjuvant therapy. Cut-off points were determined by Lausen.

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