18FDG PET/CT-derived parameters successfully predict clinical stage and prognosis of esophageal cancer.

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Abstract

Background Although ^{18}F FDG PET/CT is validated in baseline workup of esophageal cancer to detect distant metastases, it remains underused in assessing local staging and biology of the primary tumor. This study aimed to evaluate the association between ^{18}F FDG PET/CT-derived parameters of esophageal cancer, and its clinico-pathological features and prognosis. **Methods** All patients with esophageal adenocarcinoma or squamous cell cancer of operated between 2005-2014 were analyzed. Linear regression was used to identify clinico-pathologic features of esophageal cancer associated with the tumor's maximal Standardized Uptake Value (SUV_{max}), Total Lesion Glycolysis (TLG) and Metabolic Tumor Volume (MTV). ROC curve analysis was performed to precise the optimal cutoff of each variable associated with a locally advanced (cT3/4) status, long-term survival and recurrence. Kaplan Meier curves and Cox regression were used for survival analyses. **Results** High baseline SUV_{max} was associated with cT3/4 status and middle-third tumor location, TLG with a cT3/4 and cN+ status, whereas MTV only with active smoking. A cT3/4 status was significantly predicted by a SUV_{max} >8.25g/mL ($p<0.001$), TLG>41.7 ($p<0.001$) and MTV>10.70 cm³ ($p<0.01$) whereas a SUV_{max} > 12.7 g/mL was associated with an early tumor recurrence and a poor disease-free survival (median 13 versus 56 months, $p=0.030$), particularly in squamous cell cancer. **Conclusions** Baseline ^{18}F FDG PET/CT has a high predictive value of preoperative cT stage, as its parameters SUV_{max}, TLG and MTV can predict a locally advanced tumor with high accuracy. A SUV_{max} > 12.7 g/mL may herald early tumor recurrence and poor disease-free survival.

Background

Esophageal cancer is associated with aggressive lymphatic spread, resulting often in locally advanced or metastatic disease upon diagnosis [1]. Metabolic imaging with 18-Fluorodeoxyglucose Positron Emission Tomography/Computerized Tomography (^{18}F FDG-PET/CT) has been integrated into the preoperative workup of esophageal cancer for the detection of distant suspicious lesions [1–3], interval metastases [4] or assessment of response to neoadjuvant treatment [5]. Esophageal cancer workup should use three-modality staging with Computerized Tomography (CT), endoscopic ultrasound (EUS) and ^{18}F FDG PET/CT [2,3], as failure to identify locally advanced tumors (cT3/4 or N+) may lead to omission of neoadjuvant treatment before surgery, compromising patient survival [2,6]. To this day, ^{18}F FDG PET/CT-derived parameters SUV_{max} (maximum Standardized Uptake Value), TLG (Total Lesion Glycolysis) and MTV (Metabolic Tumor Volume) remain underused for the cT and N staging of the primary tumor due to the poor spatial resolution within esophageal wall layers. However, Malik et al recently demonstrated a significant predictive value of MTV in differentiating early-stage (cT1/2) versus locally advanced (cT3/4) lesions [7]. Obtaining accurate cTN staging information through ^{18}F FDG PET/CT may be of prime importance particularly where EUS is unavailable, either by lack of an expert operator, or if the tumor is obstructive (up to 19% of patients) [7].

The aim of our study was to assess the association of several clinico-pathological characteristics of esophageal cancer and the ^{18}F FDG-PET/CT derived parameters SUV_{max} , TLG and MTV, as well as to evaluate the predictive value of these parameters in survival and tumor recurrence.

Methods

All patients operated for esophageal adenocarcinoma or squamous cell cancer, with curative intent, from 2005-2014 in our tertiary referral center and a baseline ^{18}F FDG-PET/CT in the preoperative workup were included in this study. Demographic, clinical and histological data were retrieved from our prospectively maintained database.

In all patients, routine preoperative staging was performed by esophagogastroduodenoscopy, EUS and thoraco-abdominal CT scan. Since 2005 ^{18}F FDG-PET/CT was integrated in the baseline preoperative workup, according to current recommendations [2]. TNM stage was defined according to the 7th TNM classification [8]. Neoadjuvant treatment was administered for locally advanced lesions (cT3/4 and/or N+), with 5FU-platin or carboplatin-paclitaxel based chemotherapy and external beam radiation of 41-54 Gy. R0 resection was defined as the presence of tumor within 1mm of resection margins. Postoperative follow-up included a thoraco-abdominal CT scan every 4 months for the first two postoperative years and further workup in cases of suspected recurrence [9]. Early recurrence was defined as any documented recurrence in the first 12 postoperative months. Follow-up data were last updated in November 2018, to assure a minimum follow-up of 4 years for all patients.

Baseline ^{18}F FDG-PET/CT and derived parameters

Since the beginning of this study, we introduced our own PET/quality control program used in several national and international PET studies [10] until our center participated to the quality control program by EANM EARL as PET/CT Center of Excellence in October 2011, for which we have been accredited each year so far. For ^{18}F FDG-PET/CT, patients fasted for at least 6 hours before and blood glucose was measured before administration of the radiotracer (<8.5 mmol/L). Each patient received 3.5 MBq/kg of ^{18}F -FDG intravenously and remained in a calm and warm area for 1 hour. Thereafter, the patient was asked to void and subsequently was placed in the scanner. Images were acquired on PET/CT scanner (Discovery LS before 09/2011 and then Discovery D690 TOF; GE Healthcare, Waukesha, WI) with scatter and point-spread function recovery corrections. The CT scan (140 kV, 80-200 AutomA/SmartmA) was used for attenuation correction. The CT scan was followed by a PET over the same body region (2min/bed position). Two nuclear medicine physicians closely reviewed the images using for analysis an Advantage Workstation (version 4.6, GE Healthcare, Waukesha, WI) using PET VCAR to compute SUV_{mean} , SUV_{max} , TLG and MTV.

SUV_{max} was defined as the point of maximal radiotracer uptake value within the delineated tumor volume (g/mL). MTV represents the metabolically active tumor volume (cm^3), whereas TLG was computed as the product of MTV multiplied by the tumor's SUV_{mean} . In order to define the contouring margin of primary tumor, a volume of interest around the tumor was drawn carefully to incorporate the target lesion in transaxial, sagittal and coronal planes. For tumor delineation we used a 42% threshold, as it is one of the most commonly used in the literature [7,11].

Statistical analysis

Linear regression was performed to assess correlation between several clinicopathological variables and baseline SUV_{max} , TLG and MTV. For each PET-CT derived parameter, a ROC curve analysis was performed to assess whether an optimal cutoff could be associated with locally advanced lesions (cT3/4), overall survival and early tumor recurrence. Overall and disease-free survival were analyzed with the Kaplan-Meier method and log-rank test as well as and a Cox regression analysis. Exploratory survival analyses were carried out for each histological type (adenocarcinoma and squamous cell). Co-variables with a p-value<0.2 on a univariate level were entered to a backward elimination process, allowing to build the final multivariate model with the lowest AIC value. Significance level was set at $p<0.05$ and all tests were two-sided. Statistical analysis was performed with RStudio (version 3.2.3, RStudio Team 2015, Boston, USA) and SPSS (version 23.0, Chicago, USA).

Results

From the 141 patients operated in the study period, 89 had a baseline ^{18}F FDG-PET/CT in their workup (63%). Three of them were excluded from analysis because of histology other than adenocarcinoma or squamous cell; thus, the current series consists of 86 patients. Baseline patient characteristics are outlined in **Table 1**. Tumor location was distributed throughout middle, distal third and gastroesophageal junction (GEJ); sixty-three (73%) of all tumors were cT3/4 and 49 (57%) cN+. Adenocarcinoma represented 53% and squamous cell histology 47% of all lesions. During initial workup, 78 patients (91%) had an EUS, and the lesion was obstructive in 7 % of them; 94% of all tumors were FDG-avid in ^{18}F FDG-PET/CT.

Baseline ^{18}F FDG-PET/CT -derived parameters and initial tumor staging

a. SUV_{max} (maximal Standardized Uptake Value)

Median baseline SUV_{max} was 12.1 g/mL (range 2.8-48.0) for all tumors. Middle third tumor location, advanced cT and cN stage as well as squamous cell histology were associated with higher SUV_{max} values on a univariate level, however only tumor location and cT stage remained significant on multiple regression (**Table 2**). cT3/4 tumors had an expected SUV_{max} 6.61 higher than a cT1-2 lesion (β coefficient 6.61, 95%CI 2.40, 10.81, $p=0.002$), and middle third tumors an expected SUV_{max} 7.01 higher than GEJ lesions (β coefficient 7.01, 95%CI 0.71-13.32, $p=0.029$). The multivariable model presented a good fit to the data ($R^2= 0.2804$, F-statistic 4.676 on 6 and 72 DF, $p<0.0001$).

Baseline SUV_{max} presented a good prognostic value of a cT3/4 status in ROC curve analysis (**Figure 1a**). A SUV_{max} of 8.25g/mL predicted a cT3/4 lesion with a sensitivity of 83.9% and a specificity of 68.4%. Overall accuracy as indicated by the area under the curve was 81.6% (AUC=0.816, 95%CI=0.704-0.928, $p<0.001$).

b) TLG (Total Lesion Glycolysis)

Median TLG for all tumors was 122.1 (range 1-1179). Simple linear regression revealed higher TLG values for cT3/4 and cN+ tumors, and both co-variables remained significant in multivariate analysis; expected TLG values for cT3/4 tumors were 162.9 higher than cT1/2 tumors (β coefficient 162.95, 95%CI 31.39-294.51, $p=0.016$), and cN+ had a TLG increased by 145.83 compared to cN0 lesions (β coefficient 145.83, 95%CI 34.47-256.19, $p=0.010$). (**Table 3**) The model presented a good fit to the data ($R^2= 0.1852$, F-statistic 7.841 on 2 and 69DF, $p<0.001$).

ROC curve analysis identified a TLG >41.7 as the optimal cutoff to detect a cT3/4 lesion, with a sensitivity of 86.4%, a specificity of 80% and an overall accuracy of 85.2% (AUC 0.852, 95%CI 0.744-0.960, $p<0.001$) (**Figure 1b**)

c) MTV (Metabolic Tumor Volume)

Median MTV for all FDG-avid tumors was 22.7 cm³ (range 1-519). Univariate analysis identified only active smoking being associated with higher baseline MTV (β coefficient 32.81, 95%CI 4.99-70.62, $p=0.093$) and thus, no multivariable analysis was possible for this parameter.

In ROC curve analysis a baseline MTV > 10.70 cm³ was identified as the optimal cutoff to predict cT3/4 status (sensitivity 83.1%; specificity 75%, AUC 0.799, 95%CI 0.640-0.959, $p=0.01$) (**Figure 1c**).

Prognostic value of ¹⁸FDG-PET/CT -derived parameters for recurrence and patient survival

Among the three parameters studied, SUV_{max} at baseline was the only one with a significant predictive value for early tumor recurrence (**Figure 2**). A SUV_{max} ≥ 12.7 g/mL predicted early recurrence with 70.4% sensitivity and 64.6% specificity (AUC 0.660, 95% CI 0.535-0.785, $p=0.019$) (**Figure 2a**). Indeed,

patients with a $SUV_{max} < 12.7$ g/mL at baseline had a median disease-free survival (DFS) of 56 months (95%CI 7.68-104.31), versus 13 (95%CI 10.35-15.65) for those with a $SUV_{max} \geq 12.7$ g/mL ($p=0.030$) (**Figure 3**). Cox regression analysis confirmed $SUV_{max} \geq 12.7$ as an independent predictor of DFS (HR 2.54, 95%CI 1.26, 5.09, $p=0.009$), along with preoperative active smoking and pT3/4 status (**Table 4**).

When the two histological subtypes were analyzed separately, there was no significant association of SUV_{max} with DFS for adenocarcinoma. For squamous cell carcinoma, a baseline $SUV_{max} \geq 12.7$ g/mL along with pT and pN stage independently predicted worse DFS (**Table 4**).

No association was found between baseline SUV_{max} and overall survival (OS), neither on the Kaplan-Meier (**Figure 3**) nor the Cox regression analysis. In the latter, only active smoking (HR 2.30, 95% CI 1.15-4.62, $p=0.019$) and pT4 stage (HR 21.42, 95%CI 5.00- 91.72, $p<0.0001$) independently predicted OS. None of the variables remained independent predictors of OS in adenocarcinoma or squamous cell subtypes.

Median follow-up of all patients, calculated with the reverse Kaplan-Meier method, was 50 months (95%CI 45.33-54.66).

Conclusions

^{18}F FDG-PET/CT derived parameters $SUV_{max} > 8.25$ g/mL, $TLG > 41.7$ and $MTV > 10.70$ cm³ were significantly associated with locally advanced cT3/4 stage and a baseline $SUV_{max} > 12.7$ g/mL with early tumor recurrence and poor disease-free survival, particularly for squamous cell cancer. These findings need further validation to establish their predictive value in staging and prognosis of esophageal cancer. A prospective study is currently running in our institution to correlate these values with high-resolution CT and IRM characteristics of the primary tumor.

Declarations

- Ethics approval and consent to participate: The study was approved by the Lausanne University Institutional Review Board. On the basis of the general research contentment form, the need for individual consent was waived.
- Consent for publication: not applicable
- Availability of data and material: The data that support the findings of this study are available from authors upon request and with permission of the Lausanne University Ethics Committee.
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- Authors' contributions: SM and AP study design, data collection, PET/CT interpretation, statistical analysis and drafting of the manuscript. MW, PA and ND drafting and clinical review of the manuscript. JP study design, PET/CT interpretation, drafting manuscript and critical review of the

manuscript. MS study design, statistical analysis, drafting and critical review of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline demographics and preoperative workup of all patients.

Variable	N=86
Median age, years [range]	63 [38-82]
Male Gender (%)	66 (77)
Active smoking (%)	38 (44)
ASA class (%)	
1-2	61 (71)
3-4	25 (29)
Tumor location (%)	
Upper third	3 (4)
Middle third	27 (31)
Distal third	29 (34)
Gastroesophageal junction	27 (31)
Clinical T stage (cT)	
cT1-2	21 (24)
cT3-4	63 (73)
Missing data	2 (2)
Clinical N stage (cN)	
cN0	33 (38)
cN+	49 (57)
Missing data	4 (5)
Tumor histology	
Adenocarcinoma	46 (53)
Squamous cell carcinoma	40 (47)
Preoperative workup	
CT	86 (100)
EUS	78 (91)
<i>EUS non-obstructive lesion</i>	73 (85)
¹⁸ FDG PET/CT	86 (100)

<i>¹⁸FDG PET/CT -avid lesion</i>	81 (94)
Neoadjuvant treatment	71 (82)
Operative approach	
Transthoracic (Lewis)	65 (76)
Three-field (McKeown)	19 (22)
Transhiatal	2 (2)

ASA= American Society of Anesthesiology; CT= Computerized Tomography; EUS= Endoscopic Ultrasound;
¹⁸FDG PET/CT= 18-Fluorodeoxyglucose Positron Emission Tomography CT

Table 2 Linear regression analysis for baseline SUV_{max}

VARIABLE	Unadjusted	95%CI	p-value	Adjusted	95%CI	p-value
	β coefficient			β coefficient		
cT stage						
cT1-2	Ref			Ref		
cT3-4	7.76	3.64,11.87	<0.001	6.61	2.40,10.81	0.002
cN stage						
cN0	Ref			Ref		
cN+	4.12	0.29,7.95	0.038	3.28	-0.49,7.05	0.087
Tumor location						
GEJ	Ref			Ref		
Distal third	1.41	-2.99,5.80	0.532	1.59	-3.10,6.29	0.501
Middle third	6.27	1.80,10.75	0.007	7.01	0.71,13.32	0.029
Superior third	-1.42	-11.26,8.42	0.778	-1.47	-12.05,9.11	0.783
Histology						
Adenocarcinoma	Ref					
Squamous cell	3.84	0.23,7.45	0.040	-0.630	-5.84,4.58	0.810

SUV_{max}= maximal Standardized Uptake Value; GEJ= Gastroesophageal junction; 95%CI= 95% Confidence Intervals; Ref= Reference category (β coefficient=0)

Table 3 Linear regression analysis for baseline TLG

VARIABLE	Unadjusted β coefficient	95%CI	p-value	Adjusted β coefficient	95%CI	p-value
cT stage						
cT1-2	Ref			Ref		
cT3-4	198.42	61.42,335.43	0.006	162.95	31.39,294.51	0.016
cN stage						
cN0	Ref			Ref		
cN+	168.77	58.05,279.48	0.004	145.83	35.47,256.19	0.010

TLG=Total Lesion Glycolysis; 95%CI= 95% Confidence Intervals; Ref= Reference category (β coefficient=0)

Table 4 Cox regression analysis for disease-free survival (DFS)

VARIABLE	Unadjusted HR	95%CI	p-value	Adjusted HR	95%CI	p-value
All patients						
Active smoking	2.22	1.23,4.01	0.008	2.22	1.15,4.27	0.017
SUVmax>12.7g/mL	2.10	1.16,3.81	0.014	2.54	1.26,5.09	0.009
pT stage						
pT0	Ref			Ref		
pT1	0.30	0.06,1.45	0.135	0.59	0.11,3.04	0.532
pT2	1.32	0.49,3.57	0.577	1.55	0.56,4.28	0.393
pT3	2.78	1.18,6.55	0.019	3.31	1.37,8.00	0.008
pT4	11.93	2.25,63.29	0.004	7.24	1.34,39.22	0.022
Resection margins						
R0	Ref					
R+	2.47	1.04,5.89	0.041	2.09	0.77,5.68	0.147
Adenocarcinoma						
Active smoking	2.34	1.04-5.28	0.039	2.54	1.05-6.14	0.039
SUVmax>12.7g/mL	1.87	0.85-4.11	0.119	1.54	0.65-3.62	0.323
pN stage						
pN0	Ref			Ref		
pN1	5.76	2.06-16.09	<0.001	4.04	1.29-12.58	0.016
pN2	5.24	1.78-15.49	0.003	3.88	1.25-12.02	0.019
pN3	9.31	1.82-47.49	0.007	8.67	1.50-50.07	0.016
Resection margins						
R0	Ref					
R+	4.37	1.44-13.25	0.009	2.78	0.78-9.94	0.115
Squamous cell cancer						
cT stage						
cT1-2	Ref			Ref		
cT3-4	2.74	0.92-8.10	0.069	0.96	0.19-4.78	0.961

SUVmax>12.7g/mL	1.82	0.76-4.36	0.176	5.06	1.44-17.71	0.011
pT stage						
pT0	Ref			Ref		
pT1	0.84	0.16-4.33	0.833	1.23	0.21-7.17	0.816
pT2	1.95	0.56-6.76	0.290	5.67	1.34-24.01	0.018
pT3	5.97	1.95-18.29	0.002	5.05	1.10-23.16	0.037
pT4	11.75	1.17-118.29	0.037	10.67	0.93-122.39	0.057
pN stage						
pN0	Ref			Ref		
pN1	0.22	0.03-1.67	0.144	0.09	0.01-0.92	0.042
pN2	4.51	1.42-14.31	0.010	4.71	1.00-22.14	0.049
pN3	4.39	0.95-20.32	0.058	6.72	0.90-49.88	0.062

HR=Hazard Ratio; 95%CI= 95% Confidence Intervals; Ref= Reference category (HR=1); SUV_{max}= maximal Standardized Uptake Value

Figures

Figure 1

ROC curve analyses for the predictive value of 18FDG-PET/CT derived parameters in relation to a cT3/4 status. All three parameters predicted significantly cT3-4 status of the primary tumor. a) SUVmax>8.25 g/mL (sensitivity 83.9%, specificity 68.4%, p<0.001), b) TLG>41.7 g (sensitivity 86.4%, specificity 80%, p<0.001), c) MTV>10.7 cm3 (sensitivity 83.1%, specificity 75%, p=0.01).

Figure 2

ROC curve analyses for 18FDG-PET/CT derived parameters as predictors of early tumor recurrence. a) A SUVmax >12.7 g/mL was identified as the optimal threshold for early recurrence, with a sensitivity of 70.4%, specificity 63.6% (AUC 0.660, p=0.019). No optimal cutoff was defined for b) TLG (AUC 0.624, 95% CI 0.495-0.753, p=0.081) or c) MTV (AUC 0.570, 95%CI 0.431-0.709, p=0.332)

Figure 3

Baseline SUVmax as a predictor of disease-free and overall postoperative survival. a) SUVmax >12.7g/mL was a significant predictor of poor disease-free survival (median DFS 13 versus 56 months, $p=0.030$), b) but not of overall survival