Does the association of ^{18}F-FDG uptake intensity and lesion topography reveal histological phenotype and tumor differentiation in esophageal cancer?

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Abstract

In daily clinical practice, the esophageal squamous cell cancer (ESCC) is considered to be more ^{18}F-FDG avid than adenocarcinoma (EAD). To date, the few studies concerning the existence of a real metabolic difference based on esophageal cancer (EC) histology, show divergent and not definitive results. *A retrospective analysis of* ^{18}F-FDG PET/CT of 87 patients with ESCC and EAD was performed to investigate the role played by both histopathological subtype and tumor differentiation in the characterization of glucose metabolic profile of EC. Esophageal squamous cell cancer was well differentiated (WD) in 42 cases and poorly differentiated (PD) in 12 patients. Twenty-one of the 33 patients had WD EAD, while 12 had a PD EAD. The ^{18}F-FDG maximal standardized uptake value (SUV_{max}) was determined for all lesions and used for inter and intra-group comparison. *In ESCC, the SUV_{max} ranged* from 4 to 31 with a mean value of 16±6. In EAD, the SUV_{max} ranged from 2 to 25 with a mean value of 10±6. A statistically significant difference (P<0.0001) was found between ESCC and EAD. According to histological classification and tumor differentiation, we obtained the following results: a) the SUV_{max} values of WD ESCC and WD EAD were 17±5 (range:7-31) and 7±3 (range:2-12) respectively (P<0.00001), b) the SUV_{max} values of PD ESCC and PD EAD were 11±4 (range:4-19) and 17±6 (range:7-25) respectively (P<0.05). Moreover, a statistically significant difference of SUV_{max} values was found between WD and PD ESCC (P<0.005) as well as between WD and PD differentiated EAD (P<0.0001). In order to predict tumor histology (ESCC, EAD) from both SUV_{max} and lesion location, a multivariate discriminant analysis was performed on the whole population with a resulting diagnostic accuracy equal to 82% (P<0.00001). *In conclusion*, we provide additional arguments about ^{18}F-FDG uptake difference between ESCC and EAD as well as between poorly and well-differentiated forms of both EC histological subtypes.

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Introduction

Ruorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is nowadays widely applied in the management of esophageal cancer (EC). Esophageal cancer includes two major histological subtypes: the squamous cell cancer (ESCC) and the adenocarcinoma (EAD) [1-2]. Tumor ^{18}F-FDG uptake intensity is directly related to both the expression of cellular membrane glucose transporter-1 protein (Glut-1) and the cellular glycolysis, so the ^{18}F-FDG maximal standardized uptake value (SUV_{max}) could allow the estimation of the tumor glucose metabolism rate. The relationship between SUV_{max} and both tumor histological type and differentiation has been assessed for various malignancies such as lung and cervical cancer [3-4], but the literature offers limited data concerning the EC [5].

In the present study, we have thus investigated the role played by both histopathologic subtype and tumor differentiation in the glucose metabolic profile of EC.

Subjects and methods

We have performed a retrospective analysis of patients addressed to the Nuclear Medicine Department of both Strasbourg and Nancy University Hospitals for EC evaluation by PET/CT before any treatment.

Eligible patients were identified by ^{18}F-FDG PET/CT databases according to the following inclusion criteria: a) either ESCC or EAD proved by biopsy, b) tumor stage from II to IV proved by either endoscopic ultrasound (EUS) or pathologic criteria according to the TNM system of the American Joint Committee on Cancer, c) availability of unequivocal pathological information about tumor differentiation: only well differentiated (WD) and poorly differentiated (PD) tumors were selected.

We have left out of our study the patients with: a) histological types of EC different from ESCC and EAD (i.e. leimyoma, gastrointestinal stromal tumor, small cell carcinoma), b) tumor stage 0 and I according to both clinical and pathological criteria, c) either ESCC or EAD moderately differentiated, and d) history of esophageal surgery, radiotherapy or chemotherapy before PET examination.

Discovery (General Electric, Milwaukee, USA) and Biograph Duo (Siemens, Knoxville, USA) PET/CT devices were used in Strasbourg and Nancy, respectively. To obtain a serum glucose level of less than 6.6mmol/L, the patient fasted for 6h before the intravenous injection of 5MBq/kg of ^{18}F-FDG. Whole-body PET/CT acquisitions started 60min after tracer injection, including a head to mid thigh CT scan, followed by a 2-dimensional PET scan. Data from PET were reconstructed with CT-based attenuation correction. SUV_{max} was determined as follows:

SUV_{max} = [maximum pixel value in the tumor (kBq/mL)] / [injected dose (kBq)/patient weight (g)].

The maximum pixel value in the tumor was obtained by using circular regions of interest (ROI) covering the entire tumor on trans-axial slices. These regions were selected by two experienced nuclear medicine physicians (AI, PO) who had been informed about the topography of the EC previously detected by the conventional diagnostic approach.

The results are expressed as mean±SD, median and range. The Mann-Whitney U test was used for between-group comparisons. Comparison of proportions was done by the Fisher exact test. To predict the tumor histology (ESCC, EAD) from SUV_{max} and lesion location (proximal, medial and distal part of esophagus), discriminant analysis was performed. To limit bias in the number of patients correctly classified, the achieved classification, after cross-validation, was submitted to a jack-knife validation procedure. The Statistica package (STATSOFT; www.statsoft.com) was used for the statistical data analysis. A $P<0.05$ was considered statistically significant.

Results

The clinical and 18F-FDG PET results are summarized in Table 1 and Table 2 respectively.

Table 1. *Patient population clinical characteristics*

	No	Sex	Pt age	Tumor location				T		T Diff	
		(M / F)	mean±SD (range)	Up	Med	Low	LC	(II – IV)		WD	PD
ESCC	54	(39 / 15)	63±9 (49-82)	21	21	11	1	II	19	16	3
								III	32	24	8
								IV	3	2	1
EAD	33	(29 / 4)	62±11 (38-85)	1	2	21	9	II	14	11	3
								III	19	10	9
								IV	-	-	-

ESCC: esophageal squamous cell cancer; EAD: esophageal adenocarcinoma; Up: upper esophagus; Med: medial esophagus; Low: lower esophagus; LC: lower esophagus and cardia; T: tumor stage according to TNM classification [6]; T Diff: tumoral differentiation; WD: well differentiated; PD: poorly differentiated.

Table 2. *^{18}F-FDG PET results (SUV_{max}) obtained from the analysis of the whole population*

	WD EC			PD EC			
	mean±SD	median	range	mean±SD	median	range	P WD vs. PD
ESCC	17±5	16	7-31	11±4	11	4-19	< 0.0001
EAD	7±3	6	2-12	17±6	17	7-25	< 0.005
P ESCC vs. EAD		< 0.00001			< 0.05		

ESCC: esophageal squamous cell cancer; EAD: esophageal adenocarcinoma; WD: well differentiated; PD: poorly differentiated; EC: esophageal cancer.

Among the eighty-seven patients selected for this study (68 men and 19 women; age: 63±10; age range: 38-85), fifty-four (62%) and thirty-three (38%) patients were found to be affected with ESCC and EAD respectively. Esophageal SCC was well differentiated in forty-two cases and poorly differentiated in the remaining twelve patients. Twenty-one of the 33 patients had well-differentiated EAD, while 12 had a poorly differentiated EAD. Esophageal SCC was located in the proximal, medial and distal part of the oesophagus in 21, 21 and 12 cases, respectively. On the other hand, EAD was detected in the proximal, medial and distal part of the oesophagus in 1, 2 and 30 patients. As for the T grade, 33, 51 and 3 esophageal lesions were graded as T2, T3 and T4 respectively.

All ESCC and EAD primary tumours were visualised on ^{18}F-FDG PET/CT images (Fig. 1).

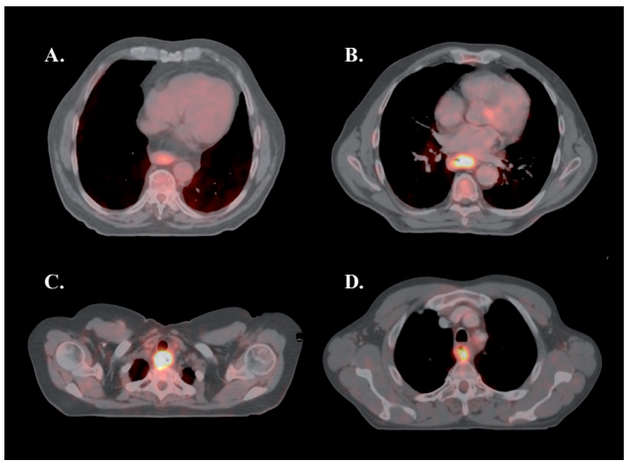

Figure 1. Esophageal well differentiated adenocarcinoma (**A**), poorly differentiated adenocarcinoma (**B**), well differentiated squamous cell cancer (**C**) and poorly differentiated squamous cell cancer (**D**). A representative image of each histological type and differentiation is reported.

In the 54 examined ESCC, SUV_{max} ranged from 4 to 31 with a mean value of 16±6. For all the EAD, SUV_{max} ranged from 2 to 25 with a mean value of 10±6. A statistically significant difference (P<0.0001) was found between ESCC and EAD.

According to both histological classification and tumor differentiation (Fig. 2): a. The SUV_{max} values of WD ESCC and EAD resulted as being equal to 17±5 (range:7-31) and 7±3 (range:2-12), respectively. A statistically significant difference was found between ESCC and EAD (P<0.00001). b. The SUV_{max} values of PD ESCC and EAD resulted as being equal to 11±4 (range:4-19) and 17±6 (range:7-25), respectively. A statistically significant difference was found between ESCC and EAD (P<0.05). c. A statistically significant difference of SUV_{max} values was found between WD and PD ESCC (P<0.005) as well as between WD and PD EAD (P<0.0001).

In order to predict tumor histology (ESCC, EAD) from both SUV_{max} and lesion location (LOC: proximal, medial and distal part of the oesophagus), a multivariate discriminant analysis was performed on the whole population (87 patients). SUV_{max} together with LOC correctly identified 43 of 54 (80%) ESCCs and 28 of 33 (85%) EAD with a global diagnostic accuracy of 82%, a sensitivity and specificity of 72% and 90%, respectively, an 85% positive predictive value, and an 80% negative predictive value (P<0.00001).

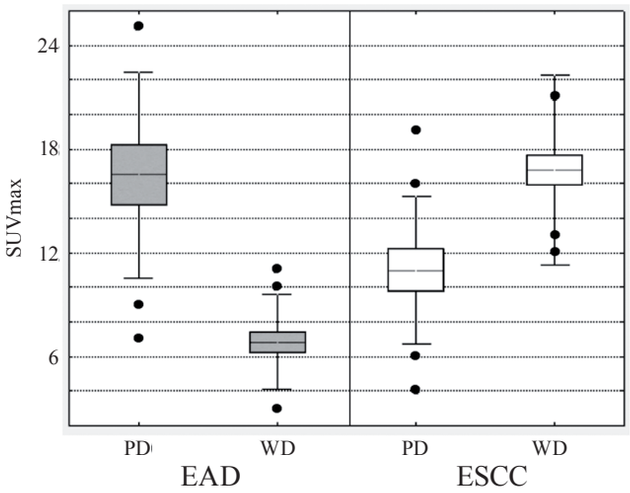

Figure 2. Box plot of SUV_{max} values obtained from the analysis of eighty-seven esophageal cancer according to both histopathology and tumor differentiation. Mean, standard error, standard deviation and outliers are graphically represented. ESCC: esophageal squamous cell cancer; EAD: esophageal adenocarcinoma; WD: well differentiated; PD: poorly differentiated.

Discussion

The SUV index presents certain limitations that are mainly due to important sources of variability in its determination [6]. In spite of that, it is still considered as the reference index whenever a quantitative evaluation is needed for diagnosis, therapy evaluation or for the purpose of prognosis. A close correlation between the ^{18}F-FDG uptake intensity and both the over expression of Glut-1 transmembrane transporters and the up-regulation of intracellular hexokynase (HK) has been previously assessed in EC [7-8]. In well-differentiated forms of lung and cervical cancer, the reduced Glut-1 and HK-II expression are directly responsible for a low ^{18}F-FDG uptake [3-4]. It is then reasonable to suppose that cellular differentiation has a key role in the modulation of the ^{18}F-FDG uptake also in EC.

In daily clinical practice, ESCC is considered to be more ^{18}F-FDG avid than EAD, the ^{18}F-FDG uptake variability of EAD appearing to be wider than that of the ESCC. But, to date, the few studies concerning the existence of a real metabolic difference based on EC histology, show divergent and not definitive results.

The first study reporting a systematic investigation about the influence of histopathologic subtype and EC grading on the ^{18}F-FDG uptake was published by Mentzel et al (2003) [5]. These authors examined forty-six patients suffering from EC (28 ESCC and 18 EAD) by the pre-therapeutic ^{18}F-FDG PET/CT technique and different degrees of tumoral differentiation. The SUV_{max} was used for ^{18}F-FDG tumor intensity evaluation. Both ESCC and EAD were characterized by an important intra-group variability in terms of SUV_{max}. Although EAD showed a mean SUV_{max} value that was moderately less than that of ESCC, the difference of uptake intensity was not statistically significant. Likewise, there was a slight but not relevant trend towards higher SUV_{max} in more dedifferentiated cancer. Unfortunately, the size of all the examined subgroups was limited, particularly those related to tumoral differentiation, so making the interpretation of the statistical results both difficult and possibly not definitive. To explain

the molecular events responsible for the increased ^{18}F-FDG uptake in EC, others [9] proposed a genetic model of esophageal cancer. Interestingly, in their preliminary results, the authors showed a significantly increased ^{18}F-FDG uptake in ESCC compared to the EAD experimental model.

Our present study is focused on an accurately selected population. Indeed, in order to minimize the PET partial volume effect on SUV_{max} estimation, tumor stage from II to IV was only considered, so excluding both tumor stage 0 and I. Moreover, in order to maximize the effect of differentiation on tumoral ^{18}F-FDG uptake, we have not included any moderately differentiated ESCC or EAD. In spite of an important heterogeneity of SUV_{max} values, the non-parametric statistical analysis applied to our data showed a significant difference between the SUV_{max} of ESCC and that of EAD. Furthermore, the good global diagnostic accuracy (82%) when predicting tumor histology from both SUV_{max} and lesion location, underlined the existence of different glucose metabolism between ESCC and EAD. The two histological EC subtypes were even more evidently discriminated by adding as a grouping factor the data regarding the tumor grading to the statistical analysis. In the EAD case, the SUV_{max} was directly related to the tumoral dedifferentiation. Conversely, the more differentiated the ESCC was, the more important the ^{18}F-FDG uptake intensity became, which agrees with the observations of others [10]. These authors investigated the expression of the neutral amino acid transporter ASCT1 and its potential correlation with the Glut-1 glucose transporter in forty-two resected EC. Interestingly, Glut-1 was expressed more often in the well differentiated ESCC than in the poorly differentiated one, representing a potential explication for our findings. Indeed, according to our results, the well differentiated ESCC were characterized from higher values of SUV_{max} than the poorly differentiated one. The same authors also showed that significantly more EAD expressed ASCT1 than ESCC [10], suggesting different metabolic needs between these two tumor histological subtypes.

One of the major limitations of the present study, directly related to its retrospective nature, is the lack of Glut-1 and HK immunohistochemical quantification, which would have allowed a better understanding of the relationship between the tumoral pathophysiological mechanisms and SUV_{max}.

In conclusion, we provide additional arguments concerning the ^{18}F-FDG uptake difference between ESCC and EAD as well as between poorly and well-differentiated forms of both EC histological subtypes. Just for common opinion, our results also suggest that poor differentiation is not necessarily matched with a high ^{18}F-FDG uptake.

The authors declare that they have no conflicts of interest.

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