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HEAD AND NECK

Is there a correlation between ^{18}F-FDG-PET standardized uptake value, T-classification, histological grading and the anatomic subsites in newly diagnosed squamous cell carcinoma of the head and neck?

Stephan K. Haerle · G. F. Huber · T. F. Hany · N. Ahmad · D. T. Schmid

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Abstract ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET)/CT imaging of squamous cell carcinoma of the head and neck (HNSCC) renders the possibility to study metabolic tumor activity by measuring FDG-uptake expressed as maximum standardized uptake value (SUV_{max}). A correlation between SUV_{max} and several factors including T-classification, histological tumor differentiation or different anatomic subsites is of potential interest in HNSCC. The aim of this study was to evaluate how metabolic tumor activity derived from FDG-PET correlates with prognostic clinical and pathological parameters including these factors. 262 patients with HNSCC undergoing PET/CT for initial staging were assessed separately for a potential correlation between SUV_{max} and T-classification, histological grading, and anatomical subsites of the primary tumor. Nonparametric testing showed a significant correlation between SUV_{max} and T-classification ($P < 0.001$). On the contrary, no statistically significant correlation was found between SUV_{max} and histological tumor grading. Furthermore, no statistical significant correlation between the different anatomical subsites and SUV_{max} were found. There was no significant correlation of SUV_{max} and tumor grading after adjustment for T-stage and anatomical localization of the tumor, neither. Conclusion: Metabolic tumor activity correlates with T-stage of HNSCC. However, histological tumor grading does not correlate with SUV_{max}. The role of primary tumor SUV_{max} as a predictor of outcome or survival remains unclear. Clinicians should therefore exercise caution in attributing any clinical importance to SUV_{max} obtained from a single PET/CT exam.

Keywords FDG-PET/CT · Standardized uptake value (SUV) · Squamous cell carcinoma · Head and neck

S. K. Haerle (✉) · G. F. Huber · N. Ahmad
Department of Otolaryngology, Head and Neck Surgery, University Hospital Zurich, Frauenklinikstrasse 24, 8091 Zurich, Switzerland
e-mail: Stephan.Haerle@usz.ch

T. F. Hany · D. T. Schmid
Division of Nuclear Medicine, Department of Medical Radiology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

Introduction

Many different staging methods for squamous cell carcinoma of the head and neck (HNSCC) have been described over the last two decades. Clinical staging includes panendoscopy and different imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), both available at most institutions. Combined functional and morphological imaging, such as ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT for staging of HNSCC has shown promising results recently [1–4]. In addition to conventional morphological imaging using CT and MRI, PET scanning allows for non-invasive study of tumor physiology [5]. There is a correlation between the uptake of FDG and the level of intracellular metabolic tumor activity, which in turn may be associated with active proliferation, invasion and incidence of loco-regional as well as distant metastases [6]. To quantify the amount of FDG uptake within a region of interest, the standardized uptake value (SUV) is used most commonly, since the measurement is standardized for injected activity, body weight and decay time. Corresponding, correlation between SUV_{max} and

several factors including T-classification, histological tumor differentiation or different anatomic subsites is of potential interest in HNSCC. Early detection of HNSCC provides a significant survival advantage and the site of primary disease is an important determinant of survival for most cancers of the head and neck [7]. Recent studies looked at different prognostic factors, whereas one of the outmost important prognostic factors for surviving HNSCC is the cervical lymph node involvement. Interestingly, Chen et al. [8] reported a higher prevalence of nodal metastases in elective neck dissections for poorly differentiated carcinomas when compared to well-differentiated tumors. Additionally, in a recent study Goerkem et al. [9] looked at the rate of occult metastases in the context of sentinel node biopsy: the less differentiated the primary was, the higher was the risk for developing occult metastases. Newer studies have included the maximum SUV (SUV_{max}) in the context for predicting outcome for patient suffering from HNSCC by looking at early SUV pattern changes after multimodality treatment [6, 10]. In their study, Suzuki et al. [10] also described a correlation between the SUV_{max} and T-stage.

The aim of this study was to evaluate how metabolic tumor activity (SUV_{max}) derived from FDG-PET correlates with prognostic clinical and pathological parameters including T-classification, histological tumor differentiation or different anatomic subsites in HNSCC at the time point of initial staging. This is important to understand if metabolic information obtained from a single PET/CT exam has the potential to serve as a predictor of disease outcome and possibly influence initial treatment strategy or if it only helps to differentiate benign from malignant changes.

Patients and methods

Two head and neck surgeons (HSK, HGF) reviewed the charts of all patients presenting for initial treatment of a HNSCC between November 2001 and December 2007, retrospectively. A board-certified physician in both nuclear medicine and radiology (SDT) reviewed records of all FDG-PET/CT exams. A total of 294 patients with histological confirmed and previously untreated HNSCC underwent FDG-PET/CT for initial staging. All patients in our study granted permission for anonymized evaluation of their medical data for scientific purposes prior to PET/CT imaging.

This patient cohort does not represent a consecutive group of all patients diagnosed with HNSCC within the given time frame, because mainly patients with advanced disease (T3/T4 and N2/N3, respectively) were referred for FDG-PET/CT to search for loco-regional lymph node metastases, distant metastases and synchronous malignant tumors.

Imaging protocol

A combined PET/CT inline system (Discovery LS or Discovery ST, GE Healthcare) was used for this study. This device integrates a PET scanner (GE Advance Nxi; GE Healthcare) with a multi-slice helical CT (LightSpeed Plus or LightSpeed 16; GE Healthcare) and permits the acquisition of co-registered CT and PET images in the same session.

Patients fasted for at least 4 h prior to scanning, which started 60 min after the injection of a standard dose of approximately 350 MBq of FDG. An oral CT contrast agent was given 75–60 min before scanning (150 mL, Micropaque, Guerbet; diluted with 850 mL water). All patients were examined in the supine position with arms down. The CT scan was acquired during breath holding or free shallow breathing. In the normal expiratory position, the following parameters were used 140 kV, 80 mA, 0.5 s tube rotation, 4.25-mm section thickness, a scan length of 867 mm with 22.5 s scan time. Acquisition of the FDG-PET scan was started immediately after the CT with an emission time of 3 min per table position resulting in a total scan time of 18 min for 6 table positions from the head to the pelvic floor.

CT data was used for attenuation correction. PET images were reconstructed using a standard 2-dimensional iterative algorithm [ordered subset expectation maximization (OSEM)].

SUV_{max} analysis

A board-certified physician in both nuclear medicine and radiology with 6 years experience in CT reading and 3 years experience in reading combined FDG-PET/CT in head and neck cancer patients determined the SUV_{max} retrospectively. Calculation of SUV_{max} was done using a commercially available workstation (Advantage workstation, software version 4.4, GE Healthcare). Before measurement, a head and neck surgeon determined the correct localization of the primary tumor retrospectively based on the knowledge of intraoperative/invasive procedures performed after the PET/CT scan. A volume of interest (VOI) was defined on screen that included the FDG uptake related to the primary tumor on multiple consecutive image sections. The value of the single voxel with the highest activity within this VOI was used for calculation of SUV_{max} (Fig. 1). The software provides this value automatically. All values were normalized to the lean body mass (LBM) of the patient. The use of LBW instead of body weight has been shown to be less dependent on the body habitus of the study population [11]. LBM was determined using a personal scale with an integrated foot-to-foot bioelectric

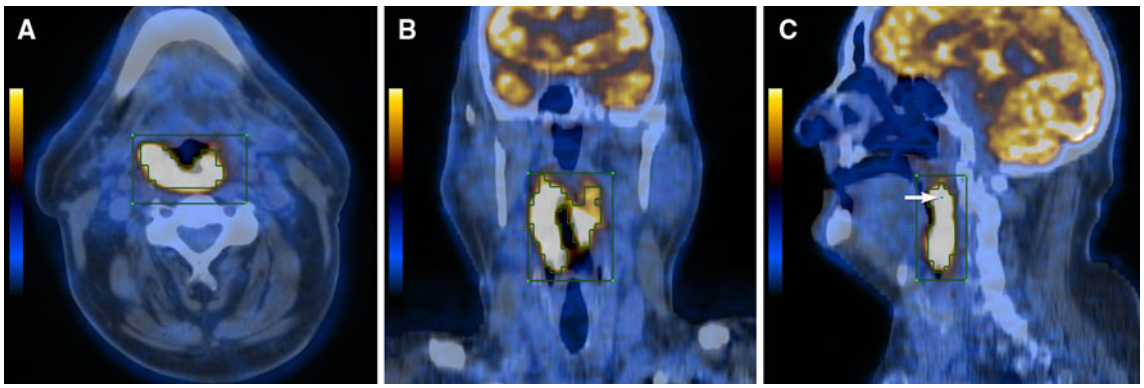

Fig. 1 Axial (**a**), coronal (**b**) and sagittal (**c**) fused FDG-PET/CT images of a 71-year old male patient with a newly diagnosed oropharyngeal carcinoma illustrating the measurement of SUVmax: the volume of interest (*green rectangles*) was set to enclose the whole tumor. A threshold of 25% of the SUVmax was chosen to outline the metabolic active tumor volume (*green line* within the *green rectangle*). The software automatically determined the hottest voxel within this volume (**c**, *white arrow*)

impedance analyzer (Tanita model 2001; Tanita, Tokyo, Japan).

Histological grading

The histological work-up of the primary was performed according to the guidelines of the Swiss Society of Pathology. All specimens were sectioned along the greatest diameter and paraffin-embedded. Whole sections were stained with hematoxylin–eosin, thus two surfaces per biopsy were available. The specimens were subdivided into well differentiated (1), moderately differentiated (2), and poorly differentiated (3).

Statistical analysis

The entire cohort was analyzed according to the following endpoints: the correlation between SUV_{max} and T-stage and the potential correlation between SUV_{max} and the histological grading with and without adjustment for anatomical localization and T-stage. Furthermore, we have analyzed the correlation between SUV_{max} and the anatomical subtype of the primary. Nonparametric testing was used. P values <0.05 were considered significant. All calculations were carried out using SPSS version 17.0 for windows.

Results

Clinical parameters

Between 2001 and 2007, a total number of 294 patients were evaluated with FDG-PET/CT for a previously untreated HNSCC. 17 patients were excluded due to missing data for SUV calculation (lean body weight, patient's size, or injected activity), 2 patients were excluded because of missing PET data, 1 patient was excluded because of CUP (cancer of unknown primary) syndrome, and 12 patients were excluded because the primary tumor was not FDG avid in PET imaging (11 patients suffering from a T1 lesion, 1 patient suffering from a T2 lesion). Finally, the number of 262 patients remained for evaluation. There was a male predominance ($n = 204$, 78%). The mean age was 60.0 years (standard deviation $\pm$ 10 years, range 36–90 years).

Localization and extension of the primary

In both male and female patients, the primary tumor was predominantly located in the oropharynx ($n = 144$, 55%), followed by the hypopharynx ($n = 51$, 19%), the larynx ($n = 33$, 13%), the oral cavity ($n = 30$, 11%), and the nasopharynx ($n = 4$, 2%). All patients presented in the advanced stages III and IV [International Union against Cancer (UICC) 1997]: $n = 41$ (16%) patients were staged as stage III, $n = 189$ (72%) patients were staged as stage IVa, and $n = 32$ (12%) patients were staged as stage IVb. T- and N-stages of all tumors are shown in Table 1.

Histological differentiation of the primary tumors

Out of the 262 primary tumors, 15 (6%) were well-differentiated SCC, 141 (54%) were moderately differentiated, and 106 (40%) of all primary tumors were found to be poorly differentiated.

Mean SUV_{max} values

SUV_{max} of all primaries was 10.7 (standard deviation $\pm$4.6, range 2.9–33.7). Mean SUV_{max} for the different anatomic subsites, the different T-stages and histological gradings are listed in Table 2.

Table 1 T- and N-stages of all patients ($n = 262$) based on all available clinical examination including panendoscopy, contrast-enhanced CT and PET/CT

Data are numbers of subjects, with percentages in parentheses

	N0	N1	N2a	N2b	N2c	N3	Total
T1	0 (0)	8 (3.1)	3 (1.1)	16 (6.1)	2 (0.8)	2 (0.8)	31 (11.8)
T2	0 (0)	10 (3.8)	0 (0)	66 (25.2)	12 (4.6)	5 (1.9)	93 (35.5)
T3	15 (5.7)	8 (3.1)	1 (0.4)	25 (9.5)	14 (5.3)	1 (0.4)	64 (24.4)
T4	11 (4.2)	10 (3.8)	2 (0.8)	23 (8.8)	23 (8.8)	5 (1.9)	74 (28.2)
Total	26 (9.9)	36 (13.7)	6 (2.3)	130 (49.6)	51 (19.5)	13 (5.0)	262 (100)

Table 2 Clinical characteristics and correlations between SUV_{max} and T-classification, histological grading, and the anatomic subsite

Characteristics	Patients[a]	SUV^{b}_{max}	*P* value
T-stage			
T1	31 (11.8)	8.3 ± 3.2 (3.0–21.8)	<0.001[c]
T2	93 (35.5)	10.2 ± 4.5 (2.9–24.7)	
T3	64 (24.4)	11.0 ± 4.3 (4.0–23.6)	
T4	74 (28.2)	11.9 ± 4.8 (3.4–33.7)	
Histological grading			
Well differentiated	15 (5.7)	12.0 ± 4.1 (3.8–16.4)	0.232[c]
Moderately differentiated	141 (53.8)	10.4 ± 4.4 (2.9–33.7)	
Poorly differentiated	106 (40.5)	10.9 ± 5.0 (3.7–29.9)	
Anatomical subsite			
Nasopharynx	4 (1.5)	11.5 ± 2.2 (8.3–13.3)	0.646[c]
Oral cavity	30 (11.5)	11.4 ± 4.4 (3.4–23.6)	
Oropharynx	144 (55.0)	10.4 ± 4.5 (2.9–33.7)	
Hypopharynx	51 (19.5)	10.7 ± 5.0 (3.8–24.7)	
Larynx	33 (12.6)	11.4 ± 5.1 (4.1–29.9)	

[a] Data are numbers of subjects, with percentages in parentheses

[b] Data are means ± SD, with range in parentheses

[c] Kruskal–Wallis test

Correlation between SUV_{max} and endpoints

Nonparametric testing using Kruskal–Wallis test showed a significant correlation ($P < 0.001$) of SUV_{max} and T-stage. There was no statistically significant correlation of SUV_{max} and histological grading ($P = 0.232$). Furthermore, no significant differences were found for mean SUV_{max} of all tumors of the same stage in relation to the anatomic subsite of the primary tumor with $P = 0.133$ for T1 tumors ($n = 31$), $P = 0.626$ for T2 tumors ($n = 93$), $P = 0.578$ for T3 tumors ($n = 64$) and $P = 0.721$ for T4 tumors ($n = 74$). There was no significant correlation between the different anatomic subsites and mean SUV_{max} ($P = 0.646$). Furthermore, there was no significant correlation of SUV_{max} and tumor grading after adjustment for T-stage and anatomical localization of the tumor.

Discussion

FDG-PET/CT marks an essential tool for initial staging in advanced HNSCC. Many important questions, such as the presence of second primaries and distant metastases can be answered at the time of diagnosis by using FDG-PET/CT [2]. Therefore, FDG-PET/CT has a direct impact on therapy decision and outcome [12]. Within the last few years, the literature shows a growing tendency to take into account metabolic information about the tumor when planning treatment of HNSCC and predicting patient's outcome [13].

The aim of this study was to assess a correlation between different clinical and pathological parameters and SUV_{max}. This may play an important role regarding the latest theories suggesting that FDG uptake of the primary tumor is related to the treatment response, and survival in HNSCC [14–17]. SUV_{max} is the most widely used parameter to measure metabolic tumor activity in oncologic FDG-PET/CT imaging. According to Machtay et al. [6] low SUV_{max} of the primary tumor was significantly associated with longer disease-free survival after radiotherapy of HNSCC in a series of 60 patients. On the contrary, Suzuki et al. [10] found no correlation between SUV_{max} and treatment outcome in HNSCC after radiotherapy in a series of 45 patients. Therefore, to elucidate the role of SUV_{max} and its possible predictive role for therapy response more distinguishable, the aim of this retrospective analysis was to assess a potential correlation between SUV_{max} and different clinical and pathological

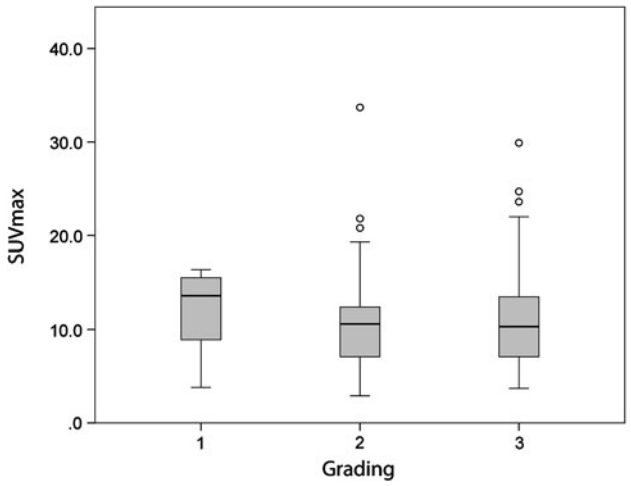

Fig. 2 Box-Plot illustrating the relation of SUV_{max} and histological grading of the primary tumors ($n = 262$). 15 (6%) tumors were well differentiated (grade 1), 141 (54%) moderately differentiated (grade 2) and 106 (40%) were poorly differentiated (grade 3)

parameters at initial staging in a large patient cohort. First, a positive correlation between SUV_{max} and T-stage can be shown ($P < 0.001$). In other words: the higher the T-stage, the higher the SUV_{max}. This is in accordance with other authors [10, 15, 18, 19]. A recent study in 627 patients with oropharyngeal carcinoma identified higher T-stage as a prognostic factor for poorer local control [20]. With regard to the histological grading of HNSCC and SUV_{max} no statistical correlation was found in our series ($P = 0.232$). This is in accordance to the findings of Suzuki et al. [10]. However, SUV_{max} values greater than 16.4 were only observed in 24 moderately and poorly differentiated tumors in our series of patients but not in well differentiated tumors (Fig. 2). The idea to look at this potential correlation lies in the fact of the helpful discriminating ability of FDG-PET/CT in the evaluation of grading of soft-tissue sarcoma [21]. Furthermore, survival is improved in patients with differentiated tumors as compared to those with poorly differentiated tumors [22]. However, summarizing our results within a relatively large patient cohort ($n = 262$), we did not find any correlation between histopathological aggressiveness and SUV_{max}. Nevertheless, there are authors proposing a cutoff SUV value of 9 correlating with worse survival [19]. The last parameter we looked at was the anatomic subsite of HNSCC. Again, no significant correlation between SUV_{max} and tumor subsite was found ($P = 0.646$). To us, this is not surprising since a T3 tonsillar carcinoma with avid FDG uptake is not comparable to a T3 carcinoma of the larynx where FDG uptake may not be as high due to the different definitions of a T3 tumor at different subsites. Further studies are needed to assess the possible value of SUV_{max} as a predictive factor of treatment outcome in HNSCC.

Conclusion

Metabolic tumor activity measured with FDG-PET/CT and expressed as SUV_{max} correlates with T-stage of HNSCC. However, histological tumor grading does not correlate with SUV_{max}. The role of primary tumor SUV_{max} as a predictor of outcome or survival remains unclear. Clinicians should therefore exercise caution in attributing any clinical importance to SUV_{max} obtained from a single PET/CT exam.

Conflict of interest The authors declare that they have no conflict of interest.

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